

UNIVERSITY OF GLASGOW

THESIS

Submitted for the Degree of

DOCTOR OF PHILOSOPHY

by

ALAN E. JEMMETT, B.Sc.

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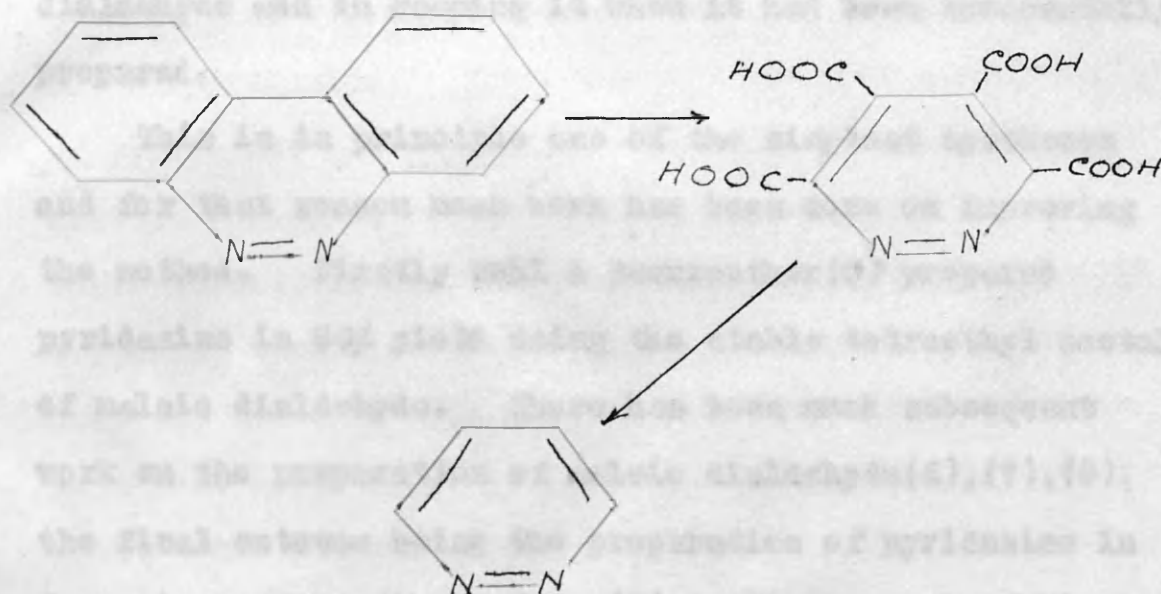


PART I.

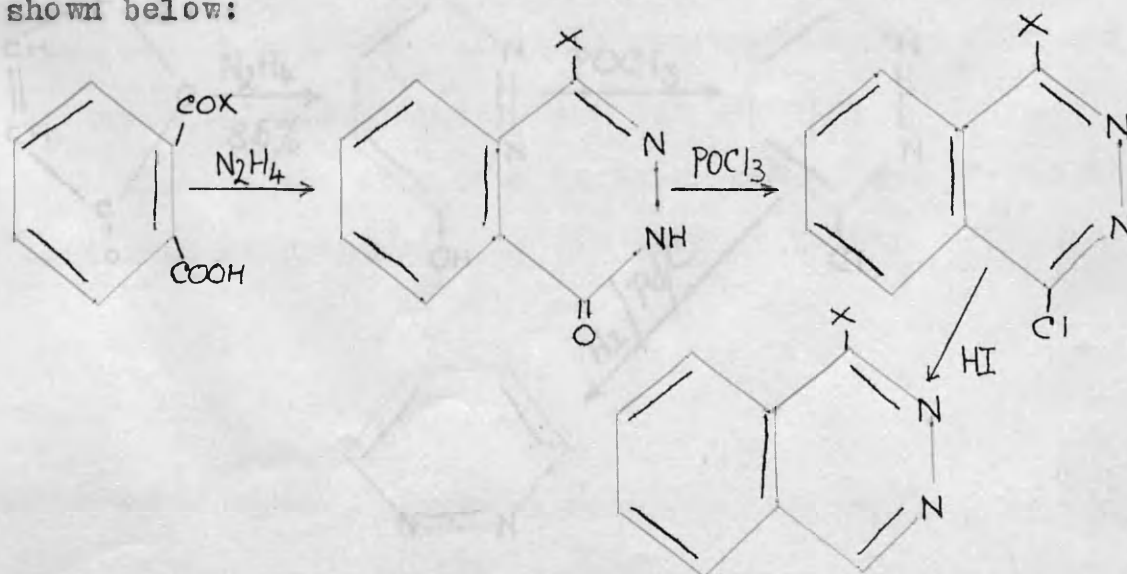
"THE CHEMISTRY OF 3:6-DICHLOROPYRIDAZINE"

## INTRODUCTION

The first recorded formation of pyridazine was by Tauber in 1895(1), from phenazone. The basis of this work was firstly oxidation and then decarboxylation as shown below:

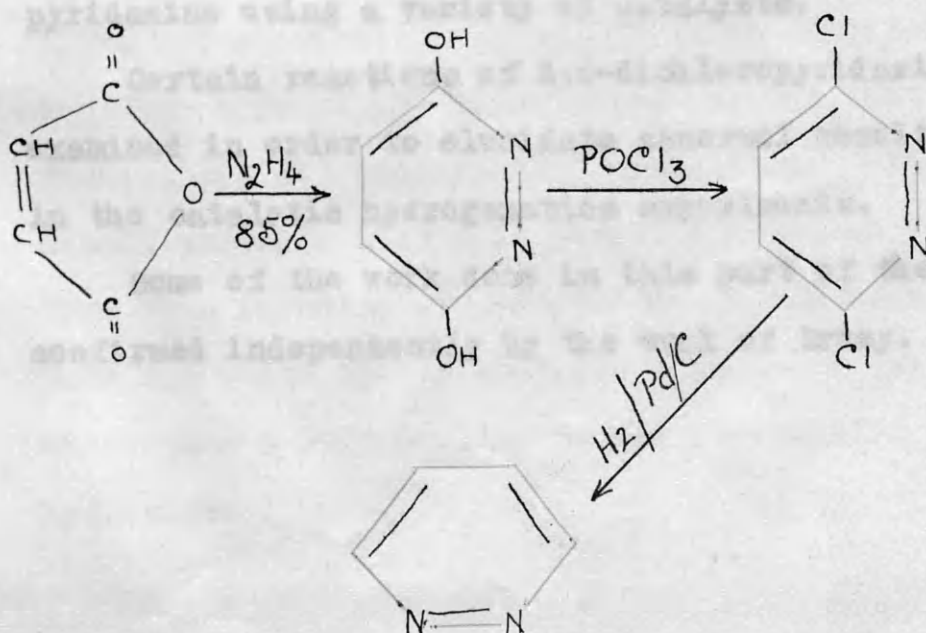


This work did not give satisfactory yields and Gabriel and Colman(2) evolved a new synthetic preparation, which can be illustrated in its general concepts by the scheme shown below:



This type of synthesis was used to prepare pyridazine itself by a method involving six steps from  $\alpha$ -keto-glutaric(3). Another early method of synthesising pyridazine was developed by Marquis(4) who prepared it in 60% yield from maleic dialdehyde and excess hydrazine. The difficulty herein was the synthesis of maleic dialdehyde and in keeping it when it had been successfully prepared.

This is in principle one of the simplest syntheses and for that reason much work has been done on improving the method. Firstly Wohl & Bernreuther(5) prepared pyridazine in 80% yield using the stable tetraethyl acetal of maleic dialdehyde. There has been much subsequent work on the preparation of maleic dialdehyde(6),(7),(8), the final outcome being the preparation of pyridazine in four stages from dihydrofuran(9). In the work of Mizzoni and Spoerri(10) maleic anhydride was used as starting material and pyridazine prepared as shown below:



The first stage had previously been investigated by Curtius and Foersterling(11) and a high yield was claimed. Further work had given increased yields(12).

On the completion of the work herein described, a series of papers were published by Druey(13),(14),(15), (16),(17) and his co-workers which gave details of the chemistry of 3:6-dichloropyridazine and the similar 3:6-dibromopyridazine. These papers also gave new synthesis of pyridazine and 6-pyridazones. The methylation of certain compounds of this series was examined and a new rearrangement noted. The ultra violet spectra of these compounds were also studied(18). Previous to this, however, the only work done on 3-halogenpyridazines was that done by Grundmann(19), and independently by Anderson (20). The preparation of 3-chloropyridazine had also been reported by Evans and Wiselogle(21).

The main object of the first part of this thesis became the study of the hydrogenation of 3:6-dichloropyridazine using a variety of catalysts.

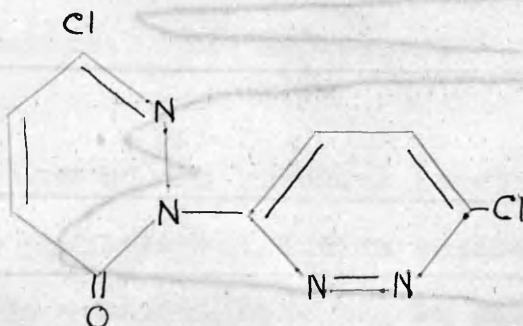
Certain reactions of 3:6-dichloropyridazine were also examined in order to elucidate abnormal results obtained in the catalytic hydrogenation experiments.

Some of the work done in this part of the thesis was confirmed independently by the work of Druey.

## DISCUSSION

Mizzoni and Spoerri's synthesis of pyridazine appears to be the best of those surveyed. In an effort to prepare pyridazine by a method analagous to theirs, 3:6-pyridazinediol was prepared by both the methods usually employed. It was found that a modification of the method of Curtius and Foersterling(11) for the preparation of 3:6-pyridazediol gave the best results, a yield of 85% being obtained in this way. This material was chlorinated by phosphorus oxychloride by a method somewhat different from that of Mizzoni and Spoerri. This modification gave a comparable yield, though a shorter reaction period was employed. The product was purified by crystallisation from petroleum to give 3:6-dichloropyridazine of m.p. =  $68^{\circ}\text{C}$ . It is of interest to note that a small fraction was less soluble in the petroleum used for the main bulk and that on crystallisation from a higher petroleum, a white solid m.p.  $150-151^{\circ}\text{C}$  was obtained. It was at first considered that this was a partially chlorinated product, but the analysis figures did not support this contention. It thus seemed probable that this compound had been derived from some impurity present in the maleic hydrazide. This was quite likely when one considered the paper by Curtius & Foersterling on the preparation of maleic hydrazide.

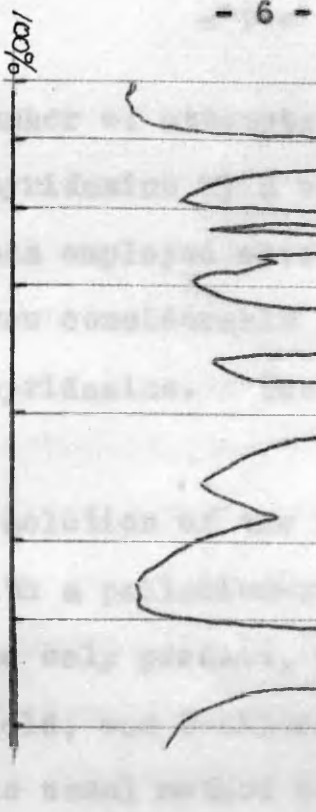
However, later reference to the work of Druey showed that this compound corresponded to that which he had found present in 3:6-dichloropyridazine and to which he had ascribed the formula shown below.



This was shown by Druey to cause a peak in the Infra-Red spectrum of 3:6-dichloropyridazine which has not been rigorously crystallised. It has however been found that 3:6-dibromopyridazine as normally prepared does not show a similar peak. The relevant infra red graphs are shown overleaf.

3,6-Dichloropyridazine

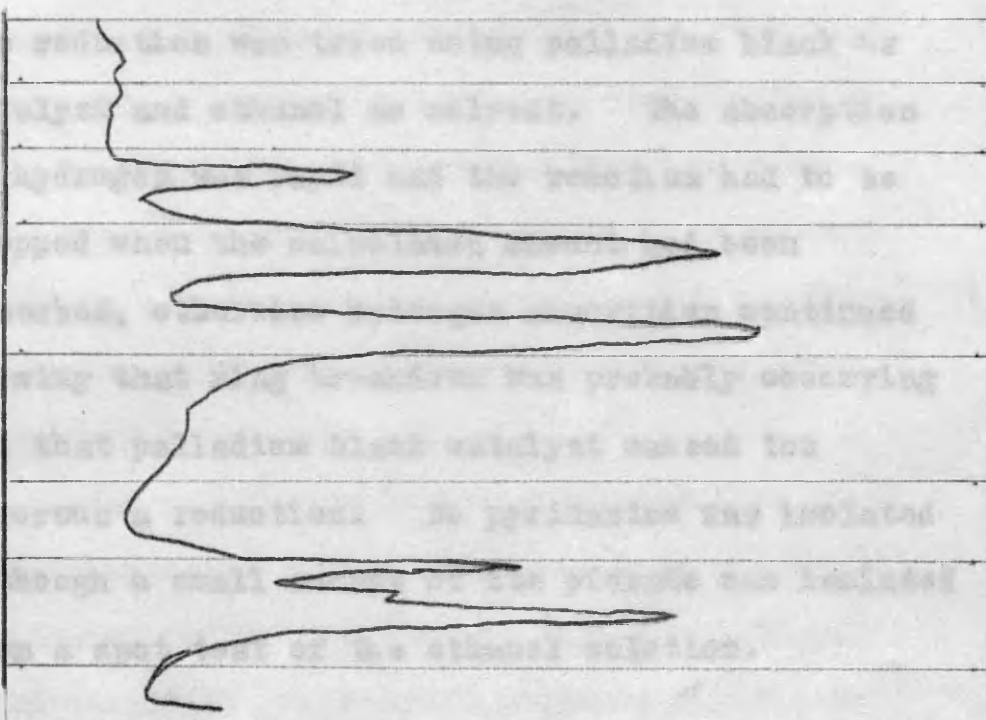
0% 1800 1700 1600 1500 1400 1300 1200 1100



3:6 Dichloropyridazine

in Nujol.

0% 1800 1700 1600 1500 1400 1300 1200 1100



3:6 Dichloropyridazine

A number of attempts were now made to reduce 3:6-dichloropyridazine by a variety of catalytic methods. The methods employed were not successful, but their study threw considerable light on the behaviour of 3:6-dichloropyridazine. The methods used are detailed below.

1. A solution of the material in ethanol was shaken with a palladium-strontium carbonate catalyst. The only product, obtained in almost theoretical yield, was 3-chloro-6-ethoxypyridazine.
2. The usual method of reduction using Raney nickel in ethanol was used. In this case no hydrogen absorption occurred and the only product isolated was 3-chloro-6-ethoxypyridazine. The Raney nickel on testing was found alkaline.
3. The reduction was tried using palladium black as catalyst and ethanol as solvent. The absorption of hydrogen was rapid and the reaction had to be stopped when the calculated amount had been absorbed, otherwise hydrogen absorption continued showing that ring breakdown was probably occurring and that palladium black catalyst caused too vigorous a reduction. No pyridazine was isolated although a small amount of its picrate was isolated from a spot test of the ethanol solution.



4. The reduction was carried out as above but the reaction was stopped when the volume necessary for the removal of only one chlorine atom had been absorbed. Pyridazine picrate was again yielded in a spot test but a considerable amount of 3:6-dichloropyridazine was also present. Thus under these conditions the reaction seems to go too vigorously and indiscriminately.
5. Dehalogenation by the method of McOmie & White(22) was also unsuccessful.
6. In a further attempt to reduce the material red phosphorus and constant boiling hydriodic acid were used. The only products of this reaction were a small amount of pyridazine (identified as picrate) and 3-iodopyridazine (solid). This iodopyridazine gave no picrate and yet when kept in ethanol solution for some days lost iodine to yield pyridazine. This is the first monoiodopyridazine recorded and its stability in ethanol should be compared to the already noted 3-chloropyridazine. The pyridazine produced was again identified as its picrate.
7. An attempt was next made to reduce 3:6-dichloropyridazine using palladium charcoal as catalyst in ethanol in the presence of baryta solution. Again ethanolic replacement occurred rapidly to yield 3-chloro-6-ethoxypyridazine.

8. Using neutral Raney nickel in ethanol in presence of magnesium oxide it was found that no hydrogenation occurred. It was also found that no ethanolic replacement occurred.

These reduction methods were thus unsuccessful as preparative methods, but they did suggest two things. Firstly, that the pyridazine ring may be broken by too vigorous reduction with palladium black, and secondly, that the chloro groups of 3:6-dichloropyridazine show marked cationoid reactivity.

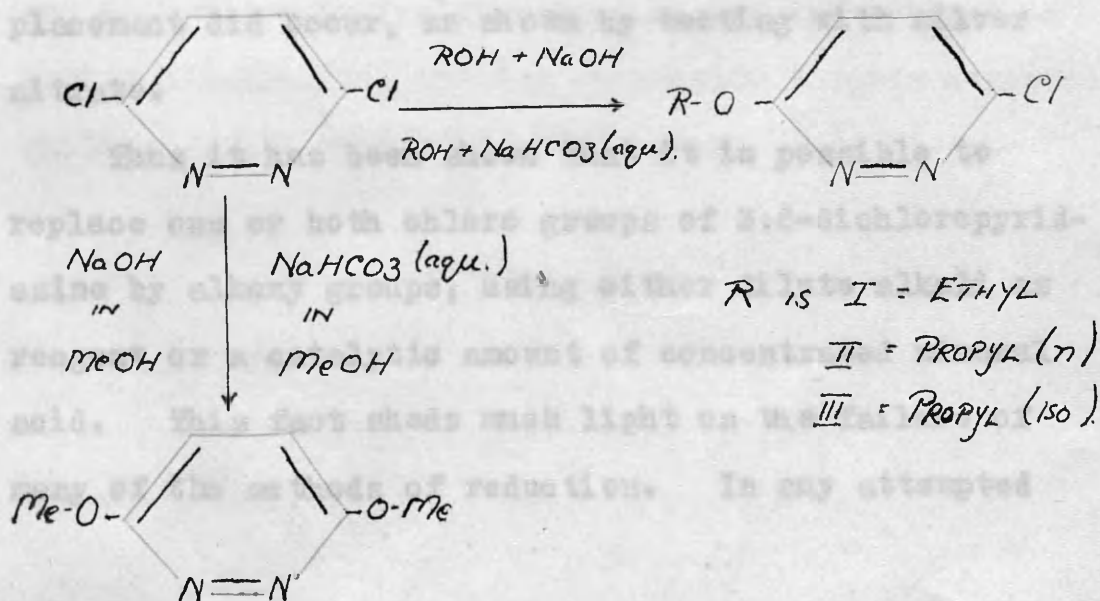
In the final experiment it had been demonstrated that with magnesium oxide as base, the usual ethanolic replacement did not occur. The reduction was therefore repeated using palladium black catalyst in ethanol and in presence of magnesium oxide. The absorption of hydrogen was theoretical in three hours. On working up the material it was found impossible to obtain pyridazine due to the formation of a stable magnesium chloride complex. All attempts to break this were unsuccessful and the method, as one of preparative interest, had to be abandoned.

Attempts to reduce the compound at ordinary pressures using palladium black in methylacetate, ether, and benzene were also unsuccessful. In each case the base used was magnesium oxide. These solvents were chosen in an attempt to reduce the solubility of the magnesium chloride produced and hence to avoid the

complex formation. In all cases little or no hydrogen absorption occurred.

The reaction of 3:6-dichloropyridazine with alcoholic caustic alkali was examined, and it was found possible to convert the compound to one of the general formula 3-alkoxy-6-chloro-pyridazine. This was true for the alcohols ethanol, n-propanol, isopropanol. Beyond propanol in the series, there was no reaction under the mild experimental conditions used. The reactions were repeated using the reaction of a dilute aqueous solution of sodium bicarbonate on an alcoholic solution of the compound, 3:6-dichloropyridazine. Again there was a rapid reaction and the products were again isolated in high yield.

The reaction, under analogous conditions, of the simplest alcohol, methanol, was somewhat different. The product was 3:6-dimethoxypyridazine.



The first paper by Druey and his co-workers was published shortly after completion of our investigation of 3:6-dichloropyridazine, and mentions this activity but gives the impression that much more drastic conditions are necessary for this reaction. This paper also mentions the possible use of these compounds as anti-spasmodic drugs.

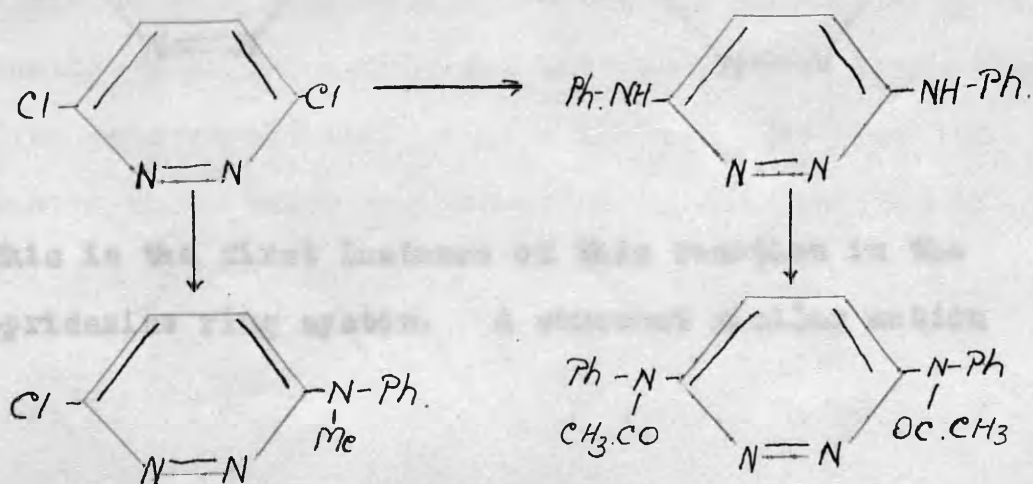
From our work it seems that beyond propanol the more vigorous conditions mentioned by Druey, Meier and Eichenberger(13) are necessary for the formation of compounds of this type.

It was later found that this type of halogen replacement also occurred using only a catalytic amount of concentrated sulphuric acid in place of the above mentioned alkalis. The reaction was however much slower, and the only product isolated was 3:6-dimethoxy-pyridazine formed under these conditions by the action of methanol. In all other cases however, halogen replacement did occur, as shown by testing with silver nitrate.

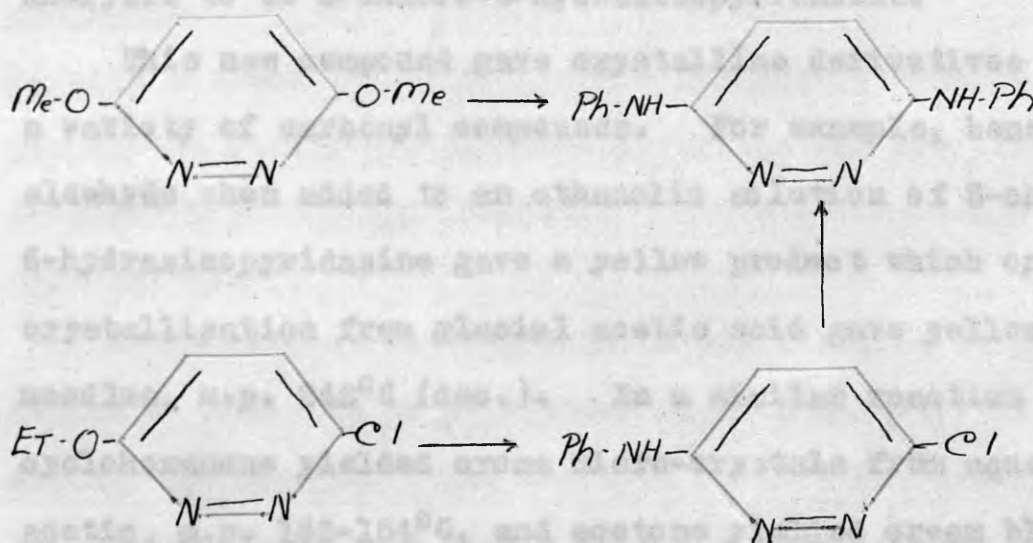
Thus it has been shown that it is possible to replace one or both chloro groups of 3:6-dichloropyridazine by alkoxy groups, using either dilute alkali as reagent or a catalytic amount of concentrated mineral acid. This fact sheds much light on the failure of many of the methods of reduction. In any attempted

reduction, where ethanol is the solvent, and dilute solutions of strong alkalis are present, the replacement reaction will occur rapidly to yield 3-chloro-6-ethoxy-pyridazine. If however, no alkali is present, as in the preparation of pyridazine under normal pressures by Mizsoni & Spoerri(10), then, at best, a low yield may well result, since as reduction occurs a strong mineral acid is produced, which, we have shown, does catalyse hydrogen replacement.

The halogen activity of 3:6-dichloropyridazine was further examined with respect to amines. It was found that the compound did not react with aqueous ammonia. This is important since it shows the probable reason for the success of Mizsoni & Spoerri's second preparation of pyridazine. That is to say, the alkali used must be sufficiently strong to remove the acid produced, but must not be strong alkali which would cause ethanolic replacement. 3:6-Dichloropyridazine reacts with aniline and with monomethylaniline when heated in presence of sodium bicarbonate, but was unreactive towards o-nitro-aniline. The scheme is shown below.



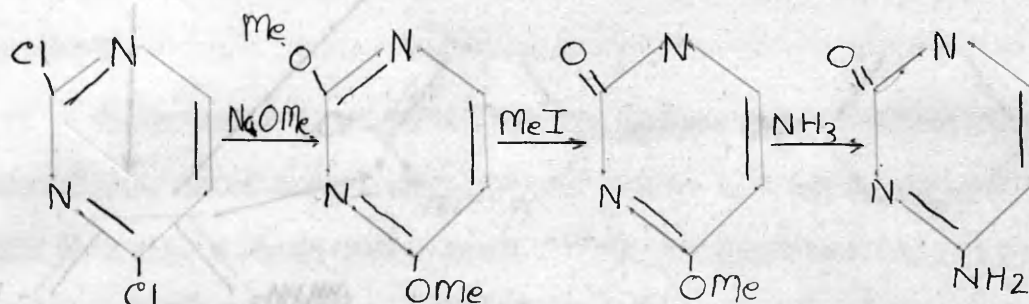
A rather unusual type of reaction was found to occur with both 3:6-dimethoxypyridazine and 3-chloro-6-ethoxypyridazine. These compounds were tested with aniline. It was found that 3:6-dimethoxypyridazine reacted when heated to about 140°C to yield 3:6-dianilinopyridazine. On the other hand when 3-chloro-6-ethoxypyridazine was heated with aniline at about 100°C, a rapid reaction occurred to yield 3-anilino-6-chloropyridazine. This shows that the ethoxy group is more readily replaced than chlorine. When 3-anilino-6-chloropyridazine was treated with a further molecule of aniline, reaction occurred at a temperature of about 140°C to yield 3:6-dianilinopyridazine.



This is the first instance of this reaction in the pyridazine ring system. A somewhat similar action

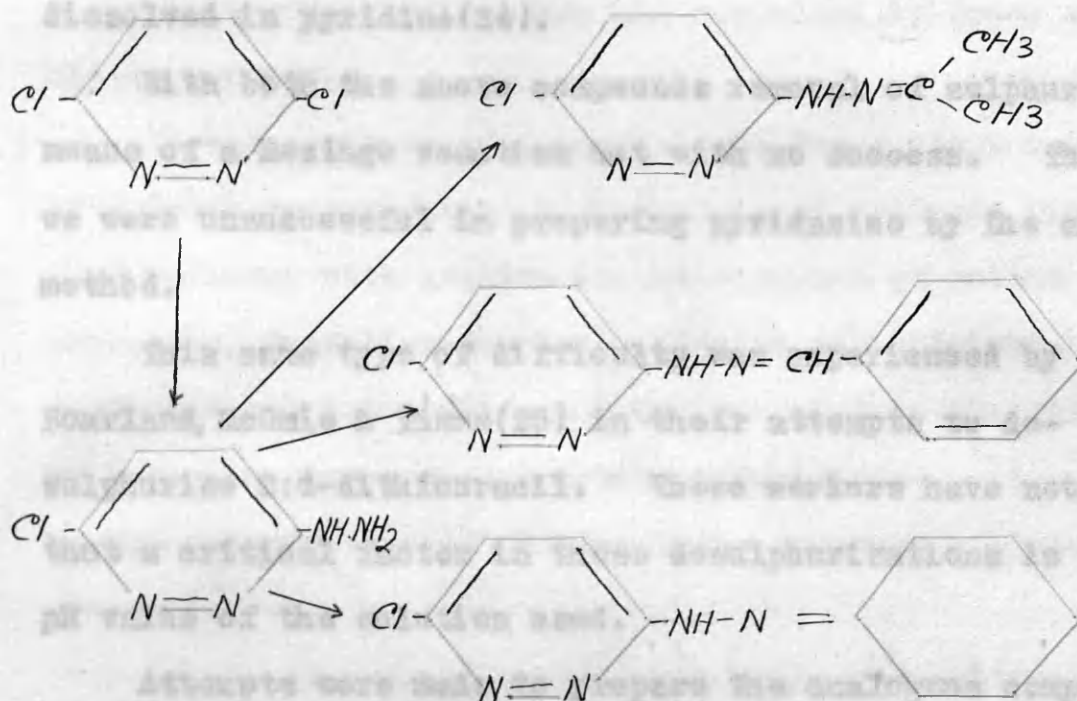


has however been recorded for the pyrimidine ring system by Flynn and his co-workers in 1953(23).



3:6-Dichloropyridazine was also found to react with an excess of hydrazine hydrate (100%) in methanol as solvent. This reaction yielded a white solid, which was shown by analysis to be 3-chloro-6-hydrazinopyridazine.

This new compound gave crystalline derivatives with a variety of carbonyl compounds. For example, benzaldehyde when added to an ethanolic solution of 3-chloro-6-hydrazinopyridazine gave a yellow product which on crystallisation from glacial acetic acid gave yellow needles, m.p.  $242^{\circ}\text{C}$  (dec.). In a similar reaction cyclohexanone yielded cream micro-crystals from aqueous acetic, m.p.  $153-154^{\circ}\text{C}$ , and acetone yielded cream blades from aqueous methanol, m.p. =  $157^{\circ}\text{C}$ . The reaction scheme shown below was supported by the analysis of all the compounds.



Since this gives crystalline derivatives with even the simple carbonyl compound acetone, it does represent a fairly good reagent for the identification of carbonyl compounds.

In a final effort to prepare 3-chloropyridazine and pyridazine itself 3:6-dichloropyridazine was converted to 3-chloro-6-mercaptopyridazine(13) and 3:6-dimercaptopyridazine(13).

3-Chloro-6-mercaptopyridazine was prepared by the action of thiourea on an aqueous alcohol solution of 3:6-dichloropyridazine. The thiourea product was decomposed by boiling in aqueous alkali to yield 3-chloro-6-mercaptopyridazine.

3:6-Dimercaptopyridazine was prepared by the action of phosphorus pentasulphide on 3:6-dihydroxypyridazine



dissolved in pyridine(24).

With both the above compounds removal of sulphur by means of a Mozingo reaction met with no success. Thus we were unsuccessful in preparing pyridazine by the above method.

This same type of difficulty was experienced by Boarland, McOmie & Timms(25) in their attempts to desulphurise 2:4-dithiouracil. These workers have noted that a critical factor in these desulphurisations is the pH value of the solution used.

Attempts were made to prepare the analogous compound 3:6-dibromopyridazine by a variety of methods. The first method employed was to reflux maleic hydrazide with phosphorus tribromide. The time of reflux was varied and, as in the preparation of 3:6-dichloropyridazine, the effect of adding dimethylaniline was investigated. It was found that the addition of dimethylaniline was not beneficial to the reaction. Attempts to catalyse the reaction by the addition of iodine as a halogen carrier were unsuccessful.

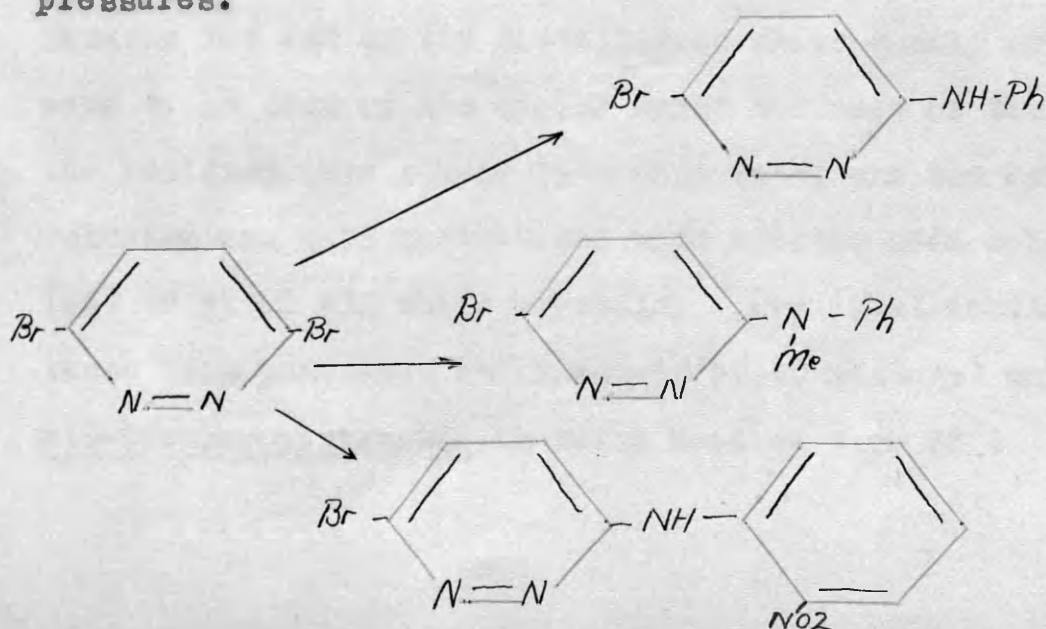
The method used by Druey and his co-workers(13) was finally used to prepare this compound. Attempts were now made to test the cationoid activity of this compound.

When 3:6-dibromopyridazine was dissolved in ethanol and treated with the calculated amount of alkali in the cold, halogen was replaced to yield 3-bromo-6-ethoxy-pyridazine. Again the halogen replacement was shown to

occur much more readily than was suggested by Druey and his co-workers.

It was again found impossible to bring about reaction of 3:6-dibromopyridazine with ammonia at ordinary pressure. When refluxed with aniline in the presence of sodium carbonate, 3-anilino-6-bromopyridazine was obtained. 3-Bromo-6-hydrazinopyridazine was prepared by the action of hydrazine hydrate on 3:6-dibromopyridazine. A cyclohexanone derivative of the resulting compound was also prepared.

It was also found possible to condense o-nitraniline with 3:6-dibromopyridazine, by heating these compounds together with a trace of sodium carbonate to a temperature of  $160^{\circ}\text{C}$ . Thus the action of 3:6-dibromopyridazine towards amines seems somewhat similar to that of 3:6-dichloropyridazine: except that it is possible, in this case to condense 3:6-dibromopyridazine with o-nitraniline. It is also of interest to note that at no time was it found possible to replace both bromine groups, under normal pressures.



Thus it was shown that the chemistry of these 3:6-dihalogenopyridazines was composed mainly of reactions wherein replacement of chlorine, or bromine, occurred. The research also shows the extreme ease with which this replacement occurs with the simple alcohols and amines.

It thus appears that, although the synthesis of pyridazine has been accomplished by reducing 3:6-dichloropyridazine, much care is necessary in such a reduction due to the extreme reactivity of the halogen atoms.

It also seems that the literature gives a mistaken idea of the reactivity of these halogen groups. In this work it has been shown that one of the chlorine atoms is very easily replaced indeed, though much more drastic conditions are usually necessary for the double replacement to occur.

EXPERIMENTAL

3:6-Pyridazinediol.- Maleic anhydride (196 g.) was dissolved in glacial acetic acid (200 ml.). Hydrazine hydrate (100%) (122.5 g.) was added dropwise with mechanical stirring, the vigour of the reaction being controlled by cooling the mixture in water. The yellow solid thus obtained consisted of a variety of products. This mixture was made into a slurry with water and heated on a steam bath, with addition of ethanol until solution was effected. The solution was now heated for a further thirty minutes and then allowed to crystallise. This yielded 3:6-Pyridazinediol as a white solid m.p.  $298^{\circ}\text{C}$  (darkening at  $280^{\circ}\text{C}$ ) (190.48 g. 85%).

3:6-Dichloropyridazine.- 3:6-Pyridazinediol (56 g.) was dissolved in phosphorus oxychloride (350 g.) and the whole was mechanically stirred and heated at  $100^{\circ}\text{C}$ , under anhydrous conditions for two hours. A black viscous material was thus obtained from which excess of phosphorus oxychloride was removed by vacuum distillation at  $60^{\circ}\text{C}$ . Towards the end of the distillation white needle crystals were to be seen on the cooler upper surfaces of the vessel. The residues were poured into cold water and the resulting solution was then neutralised with caustic soda solution (5N) to yield off white crystals. Recrystallisation of these from petroleum ether (40-60/60-80 mixture) gave 3:6-Dichloropyridazine as white needles m.p.  $68^{\circ}\text{C}$

(48.4 g. 65%). Extraction of the residual alkaline liquors with ether yielded a further crop which on recrystallisation as above gave m.p.  $68^{\circ}\text{C}$  (3.7 g. 5%). Some of the crude product was insoluble in the solvent used and was later recrystallised from petroleum ether (100/120) to give white needles m.p.  $150-151^{\circ}\text{C}$  (Found C, 39.16: H, 1.65 : N, 28.6 %).

3:6-Dimethoxypyridazine.- 3:6-Dichloropyridazine (1.5 g.) in methanol (3 ml.) was added to a slight excess of a concentrated solution of potassium hydroxide in methanol. The mixture which immediately became red in colour was allowed to stand for thirty minutes and was then filtered free from potassium chloride. The filtrate was then poured into water and the mixture then extracted with ether. The extract yielded a white solid which after crystallisation from petroleum ether (40/60) gave 3:6-Dimethoxypyridazine as white platelets m.p.  $105^{\circ}\text{C}$  (1.3 g. 90%) (Found: C, 51.16: H, 5.49: N, 19.5.  $\text{C}_6\text{H}_8\text{O}_2\text{N}_2$  requires C, 51.42: H, 5.75: N, 19.99%).

This experiment was repeated using 3 drops of concentrated sulphuric acid as catalyst instead of the alkali.

This gave 3:6-Dimethoxypyridazine m.p.  $105^{\circ}\text{C}$  (0.9 g. 60%).

3-Chloro-6-ethoxypyridazine.- 3:6-Dichloropyridazine (1.5g.) dissolved in ethanol (3 ml.) was added to a slight excess of a concentrated solution of potassium hydroxide in ethanol. The solution, which became red in colour, was

allowed to stand for thirty minutes and was then filtered free from potassium chloride. The mixture was poured into water and extracted with ether. The extract yielded a white solid which after recrystallisation from petroleum ether (40/60) gave 3-Chloro-6-ethoxypyridazine as white needles m.p. 59-62°C (1.43 g. 90%) (Found: N, 17.46.  $C_6H_7ON_2Cl$  requires N, 17.67%).

3-Chloro-6-ethoxypyridazine.- This was isolated in good yield from an attempted reduction of 3:6-dichloropyridazine using Raney nickel in ethanol even when no alkali as such was present.

3-Chloro-6-ethoxypyridazine.- This compound was also produced when hydrogenation was attempted using palladium on strontium carbonate (5%) as the catalyst.

3-Chloro-6-ethoxypyridazine.- This compound was finally prepared in a yield of 90% by the action of dilute sodium carbonate solution on a solution of the 3:6-dichloropyridazine in ethanol.

3-Chloro-6-propoxypyridazine.- 3:6-Dichloropyridazine (1.5 g.) was dissolved in n-propanol (3 ml.) and was added to a slight excess of a solution of potassium hydroxide in n-propanol. The solution was allowed to stand for thirty minutes and was then poured into water. The aqueous solution was then extracted with ether and this extract yielded a white solid. Crystallisation from petroleum ether (40/60) gave 3-Chloro-6-propoxypyridazine as white

needles m.p.  $69^{\circ}\text{C}$  (1.38 g. 80%) (Found: N, 16.34

$\text{C}_7\text{H}_9\text{ON}_2\text{Cl}$  requires N, 16.24%).

3-Chloro-6-isopropoxy pyridazine.- The above experiment was repeated using isopropanol instead of n-propanol.

This yielded 3-Chloro-6-isopropoxy pyridazine as white needles m.p.  $83-84^{\circ}\text{C}$  (Yield = 80%) (Found: C, 48.73:

H, 5.26: N, 16.13.  $\text{C}_7\text{H}_9\text{ON}_2\text{Cl}$  requires C, 48.71: H, 5.26: N, 16.24%).

3-Chloro-6-tertiarybutoxy pyridazine.- 3:6-Dichloropyridazine (1.5 g.) was dissolved in a small amount of tertiary butyl alcohol (3 ml.) and added to a small excess of a solution of potassium hydroxide in tertiary butanol. The solution became slightly red in colour but on working up in the manner above described the only product was 3:6-dichloropyridazine (1.35 g. 90%).

3:6-Dianilinopyridazine.- 3:6-Dichloropyridazine (1.0 g.) was dissolved in aniline (1.24 g.) and the mixture was heated in an oil bath to a temperature of  $138^{\circ}\text{C}$ . A brisk effervescence occurred. On cooling, a yellow solid was obtained. This was washed with dilute sodium carbonate and crystallised from ethanol to yield 3:6-Dianilinopyridazine as yellow platelets m.p.  $237^{\circ}\text{C}$  (1.6 g. 60%) (Found C, 73.05: H, 5.14: N, 21.42.  $\text{C}_{16}\text{H}_{14}\text{N}_4$  requires C, 73.27: H, 5.38: N, 21.36%). This product was converted to its monoperate in ethanol. This crystallised as yellow needles m.p.  $256^{\circ}\text{C}$  (Found C, 53.8:

H, 3.5.  $C_{16}H_{14}N_4(C_6H_3O_7N_3)$  requires C, 53.78: H, 3.49% .

The compound was also converted to its acetyl derivative by boiling in acetic anhydride for ten minutes. This yielded blade crystals m.p.  $187^{\circ}C$  (Found: N, 16.10.

$C_{20}H_{18}O_2N_4$  requires N, 16.18%).

3:6-(o-Nitranilino)pyridazine.- Following the above scheme, no reaction was noted between o-nitraniline and 3:6-dichloro-pyridazine.

3-Chloro-6-methylanilinopyridazine.- 3:6-Dichloro-pyridazine (1.5 g.) was dissolved in monomethyl aniline (1.1 g.) and sodium carbonate (0.5 g.) was added. The mixture was then heated to  $160^{\circ}C$ . A brisk effervescence occurred. On cooling a brownish residue was obtained. This was washed with acetic anhydride and recrystallisation from ethanol then gave 3-Chloro-6-methylanilinopyridazine as yellow micro-needles m.p.  $90^{\circ}C$  (1.0 g. 45.5%) (Found: C, 60.00: H, 4.53.  $C_{11}H_{10}N_3Cl$  requires C, 60.13: H, 4.59%).

3:6-Dianilinopyridazine.- 3:6-Dimethoxypyridazine (1.4 g.) was added to aniline (1.9 g.) and sodium carbonate (1.0 g.) and the mixture was heated on an oil bath to a temperature of  $138^{\circ}C$ . A brisk effervescence occurred and the mixture darkened. The product was washed with hot dilute sodium carbonate solution and on crystallisation from ethanol gave 3:6-Dianilinopyridazine as green-yellow platelets m.p.  $237^{\circ}C$  m.m.p. with an authentic specimen  $237^{\circ}C$  (2.1 g. 80%).



3-Anilino-6-chloropyridazine.- 3-Chloro-6-ethoxypyridazine (1.6 g.) was added to a mixture of aniline (0.97 g.) and sodium carbonate (0.5 g.) and the whole was then heated to 100°C. A brisk effervescence then occurred. The product was again washed with hot dilute sodium carbonate solution and on recrystallisation from ethanol yielded 3-Anilino-6-chloropyridazine as white platelets m.p. 185-186°C (1.44 g. 70%) (Found: C, 58.19; H, 3.71; N, 20.54.  $C_{10}H_8N_3Cl$  requires C, 58.41; H, 3.92; N, 20.44%).

On treating this compound in the manner described above with another mole of aniline, reaction occurred at 138°C to yield 3:6-Dianilinopyridazine.

Attempts to prepare Pyridazine.- A series of reduction methods were employed in an attempt to obtain pyridazine from 3:6-Dichloropyridazine.

(a). Palladium on strontium carbonate (2.5 g. 5%) was added to a solution of 3:6-dichloropyridazine (1.5 g.) in ethanol and the mixture shaken for thirty minutes. The only product isolated was 3-Chloro-6-ethoxypyridazine m.p. 59-62°C (1.4 g. 90%)

(b). A similar result was obtained using 3:6-Dichloropyridazine (1.5 g.) in ethanol containing Raney nickel (0.5 g.). During this attempted hydrogenation there was no absorption of hydrogen over a period of two hours and the only product was 3-Chloro-6-ethoxypyridazine (1.3 g. 80%).

(c). The reduction was also tried in the usual manner for catalytic hydrogenations using palladium black as catalyst and ethanol as solvent. The absorption of hydrogen was rapid and the reaction was stopped when the volume calculated for the removal of both chloro-groups had been absorbed. No pyridazine could be isolated although a spot test with picric acid on the ethanol solution did yield a small amount of pyridazine picrate m.p.  $172^{\circ}\text{C}$  (m.m.p. with an authentic specimen  $172^{\circ}\text{C}$ ). No other products were isolated.

(d). Reduction was carried out as above but the reaction was stopped when the volume of hydrogen necessary for the removal of only one chlorine atom had been absorbed. Even at this stage a considerable amount of 3:6-dichloropyridazine was isolable, thus showing that hydrogenation was proceeding indiscriminately.

(e). Dehalogenation of 3:6-Dichloropyridazine by the method of McOmie and White(22) was also unsuccessful.

(f). 3:6-Dichloropyridazine (5.0 g.) was mixed with red phosphorus (5.0 g.) and constant boiling hydriodic acid (30 ml.). The mixture was stirred under reflux for two and a half hours. The mixture was then filtered free from red phosphorus and the dark liquors obtained were evaporated to dryness under vacuum at  $100^{\circ}\text{C}$ . The solid thus produced was dissolved in caustic soda solution and this was then subjected to a constant ether extraction.

On evaporation of the ether a dark solid was obtained. This was then extracted with petroleum ether (60/80) leaving a small amount of dark liquid which was insoluble in the petroleum. This residue was tested with picric acid in ethanol solution. This yielded pyridazine picrate m.p.  $172^{\circ}\text{C}$ . The petroleum ether extract yielded 3-Iodopyridazine as white needles m.p.  $123^{\circ}\text{C}$  (dec.) (Found: N, 14.53: I, 62.07.  $\text{C}_4\text{H}_3\text{N}_2\text{I}$  requires N, 13.6: I, 61.61%). This substance gave no picrate. The yields in both cases were very small.

On dissolving 3-iodopyridazine in ethanol and allowing to stand exposed to ordinary light, the solution rapidly became darker and on testing it with picric acid in ethanol a pure specimen of Pyridazine picrate was obtained.

(g). An attempt was next made to reduce 3:6-dichloropyridazine in ethanol as solvent using palladium charcoal as catalyst in the presence of baryta solution. Again ethanolic replacement occurred rapidly to yield 3-Chloro-6-ethoxypyridazine in a yield of 90%.

(h). An attempt to reduce 3:6-dichloropyridazine in ethanol using Raney nickel (neutral) as catalyst in the presence of magnesium oxide showed that there was no uptake of hydrogen and no ethanolic replacement occurred.

(i). The above experiment was repeated using palladium black as catalyst instead of Raney nickel. The absorption of hydrogen was theoretical in three hours. On working

up the material it was found impossible to obtain pyridazine due to the formation of a stable magnesium chloride complex. Thus evaporation of the reaction mixture yielded only a solid which was stable to alkali and which was very insoluble in ether.

(j). The above experiment was repeated in a variety of solvents in an effort to preclude the formation of the above mentioned complex. The solvents used were methyl acetate, ether and benzene. In all cases little or no hydrogen absorption occurred.

3-Chloro-6-hydrazinopyridazine.- 3:6-Dichloropyridazine (1.5 g.) was dissolved in ethanol (20 ml.) and hydrazine hydrate (100%) (0.5 g.) was added. The mixture was refluxed for one hour. On cooling a white solid was obtained which on crystallisation from methylacetate and petroleum ether (40/60) (2:1) gave 3-Chloro-6-hydrazinopyridazine as white micro-crystals m.p.  $139^{\circ}\text{C}$  (1.2 g. 85%) Found: C, 33.06; H, 3.62; N, 38.93.  $\text{C}_4\text{H}_5\text{N}_4\text{Cl}$  requires C, 33.21; H, 3.49; N, 38.74%).

This compound in ethanol was treated with benzaldehyde to yield a Hydrazone which was recrystallised from glacial acetic acid to give yellow needles m.p.  $245^{\circ}\text{C}$  (dec.) (Found: C, 56.67; H, 3.85; N, 23.99.  $\text{C}_{11}\text{H}_9\text{N}_4\text{Cl}$  requires C, 56.78; H, 3.90; N, 24.08%).

Treatment with cyclohexanone in ethanol also yielded a Hydrazone which was recrystallised from aqueous acetic

acid to yield cream micro-crystals m.p. 153-154°C

(Found: C, 53.47: H, 5.71: N, 24.99.  $C_{10}H_{13}N_4Cl$  requires C, 53.45: H, 5.83: N, 24.94%).

A further Hydrazone was produced by treating a solution of 3-chloro-6-hydrazinopyridazine in methanol with the calculated amount of acetone. This gave a product which crystallised from methanol as cream blades m.p. 157°C (Found: C, 45.74: H, 4.68: N, 30.14.  $C_7H_9N_4Cl$  requires C, 45.54: H, 4.91: N, 30.35%).

3-Amino-6-chloropyridazine.- 3:6-Dichloropyridazine (1.5 g.) was refluxed with excess ammonia solution (0.88) for two hours. There was no reaction and 3:6-Dichloropyridazine was isolated in theoretical yield.

3:6-Dibromopyridazine.- 3:6-Pyridazinediol (9.0 g.) was powdered and mixed with phosphorus pentabromide (70 g.) and the resultant mass was then heated on a hot plate for one and a half hours. The mixture first melts and then goes solid again. The solid thus obtained was added to water and the resultant was then recrystallised from aqueous ethanol to yield 3:6-Dibromopyridazine as cream blades m.p. 117-118°C.

3-Amino-6-bromopyridazine.- 3:6-Dibromopyridazine (2.4 g.) was refluxed with excess ammonia solution (0.88) for two hours. There was no reaction and 3:6-Dibromopyridazine was isolated in almost theoretical yield (2.2 g. 91%).

3-Anilino-6-bromopyridazine.- 3:6-Dibromopyridazine (2.4 g.) was mixed with aniline (0.93 g.) and sodium carbonate (0.53 g.). The mixture was then heated to 160°C for thirty minutes. A brisk effervescence took place and the mixture darkened. Crystallisation of the product from ethanol (90%) yielded 3-Anilino-6-bromopyridazine as fawn micro-crystals m.p. 178°C (1.75 g. 70%) (Found: C, 47.77: H, 3.31: N, 17.20.  $C_{10}H_8N_3Br$  requires C, 48.02: H, 3.22: N, 16.8%).

This product was characterised as its picrate which crystallised from ethanol as yellow micro-needles m.p. 180-181°C (Found: N, 17.66.  $C_{10}H_8N_3Br \cdot C_6H_3O_7N_3$  requires N, 17.55%).

3-Bromo-6-(o-nitranilino)pyridazine.- 3:6-Dibromopyridazine (1.0 g.) was mixed with an equivalent amount of o-nitraniline and the mixture was heated, along with the requisite amount of sodium carbonate on an oil bath. Heating was continued till a temperature of 160°C was attained. A brisk effervescence took place and the melt became darker. After cooling, the solid was recrystallised from ethanol to yield 3-Bromo-6-(o-nitranilino)pyridazine as golden orange platelets m.p. 158°C (dec.) (0.9 g. 70%) (Found: C, 40.84: H, 2.12: N, 19.16.  $C_{10}H_7O_2N_4Br$  requires C, 40.70: H, 2.39: N, 18.99%).

3-Bromo-6-ethoxypyridazine.- 3:6-Dibromopyridazine (2.4 g.) was dissolved in ethanol (5 ml.) and added to a slight

excess of potassium hydroxide dissolved in ethanol.

The reaction mixture was allowed to stand for 15 minutes and then poured into water. Extraction of the aqueous solution with ether and subsequent evaporation gave a whitish product which crystallised from petroleum ether (40-60) to give 3-Bromo-6-ethoxypyridazine as long white laminae m.p.  $83^{\circ}\text{C}$  (1.73 g. 85%) (Found: C, 35.44: H, 3.68: N, 13.93.  $\text{C}_6\text{H}_7\text{ON}_2\text{Br}$  requires C, 35.49: H, 3.47: N, 13.80%).

This reaction was also carried out using sodium carbonate solution (5N) in place of the potassium hydroxide. The mixture was shaken for one hour. The yield was 70%.

3-Bromo-6-hydrazinopyridazine.- 3:6-Dibromopyridazine (2.4 g.) was dissolved in ethanol (20 ml.) and hydrazine hydrate (100%) (0.8 g.) was now added. The solution was heated for 15 minutes and then set aside to cool. On standing, a cream solid was formed. This product, after recrystallisation from aqueous ethanol gave 3-Bromo-6-hydrazinopyridazine as micro-needles, m.p. =  $145-146^{\circ}\text{C}$  (Found: C, 25.22: H, 2.97: N, 29.56.  $\text{C}_4\text{H}_5\text{N}_4\text{Br}$  requires C, 25.41: H, 2.67; N, 29.64%).

Cyclohexanone derivative.- Cyclohexanone was added to a solution of the above compound in ethanol and the mixture was boiled for ten minutes. The cream solid thus obtained was recrystallised from aqueous ethanol to yield the cyclohexanone derivative as cream micro-crystals m.p. =  $149^{\circ}\text{C}$  (Found: C, 44.79: H, 4.81: N, 20.96.  $\text{C}_{10}\text{H}_{13}\text{N}_4\text{Br}$  requires

C, 44.62: H, 4.87: N, 20.82%).

3-Chloro-6-mercapto-pyridazine.- 3:6-Dichloropyridazine (1.5 g.) and thiourea (0.76 g.) were suspended in water (5.0 ml.). The mixture was refluxed for 2 hours. Caustic soda (0.6 g.) in water (60 ml.) was then added and the mixture was refluxed a further 2 hours. On Cooling the thiol separated. The crude product was recrystallised from benzene to give yellow microcrystals m.p. 138°C.

3:6-Dimercaptopyridazine.- 3:6-Pyridazinediol (3.7 g.) was dissolved in pyridine (175 ml.) and phosphorus pentasulphide was added. The whole was stirred under reflux for 1½ hours. The mixture was cooled and poured onto caustic soda (66 g.) in water (500 ml.). Aqueous layer was neutralised with glacial acetic. This gave a yellow solid which was crystallised by dissolving in alkali and reprecipitating with acid to give 3:6-Dimercaptopyridazine as yellow micro-crystals m.p. 242°C (1.65 g. 35%).

3-Chloropyridazine.- 3-Chloro-6-mercaptopyridazine (1.47 g.) was suspended in water (50 ml.) and ammonia (0.88) (1.5 g.) was then added. Raney nickel catalyst (7.0 g.) was then added and the reaction mixture was refluxed for six hours. The raney nickel was filtered off from the hot solution. The only product isolable from this reaction mixture was the starting material 3-chloro-6-mercaptopyridazine (1.1 g. 75%).



Pyridazine.- 3:6-Dimercaptopyridazine (1.44 g.) was suspended in water (50 ml.) and ammonia (0.88) (1.5 g.) was added. Raney nickel catalyst (7.0 g.) was then added and the mixture was refluxed for six hours. The nickel was filtered from the hot solution. No product crystallised on cooling. On rendering acid with hydrochloric acid (5 N) a yellow product was obtained. This was 3:6-dimercaptopyridazine, m.p.  $242^{\circ}\text{C}$  (1.1 g. 76%).

## SUMMARY

The reactivity of 3:6-Dihalogenopyridazines towards alcohols and amines has been demonstrated and an unusual replacement reaction has been shown to occur with aniline and 3-chloro-6-ethoxypyridazine.

It has also been shown that the introduction of a group in place of one of the halogen atoms renders the replacement of the other halogen extremely difficult.

The catalytic hydrogenation of 3:6-Dichloropyridazine has also been studied.

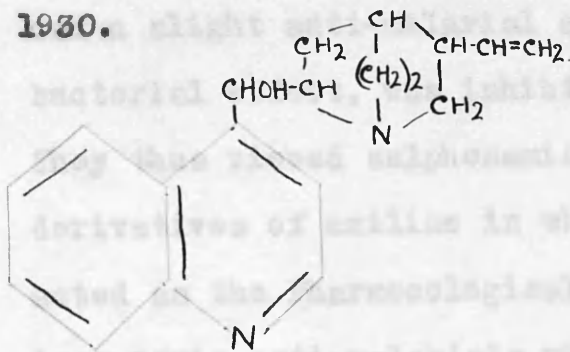
PART II.

"ATTEMPTS TO SYNTHESISE DIAZACARBAZOLES"

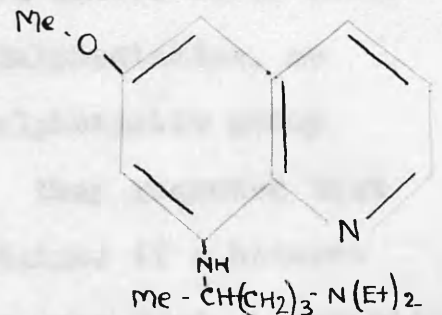
# INTRODUCTION

The therapeutic value of quinine in the treatment of malaria has long been known, the alkaloid having been isolated in 1820 by Pelletier and Caventou. In 1891, Erlich noted that methylene blue had a similar though weaker activity as an anti-malarial.

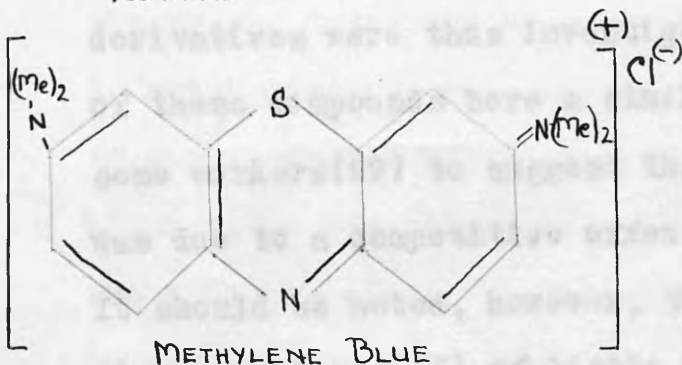
With this knowledge, later workers prepared numerous quinoline and acridine derivatives in a search for synthetic anti-malarials. This resulted in the synthesis of Pamaquin by Schulemann in 1926 and Mepacrine by Mauss and Mietzsh in 1930.



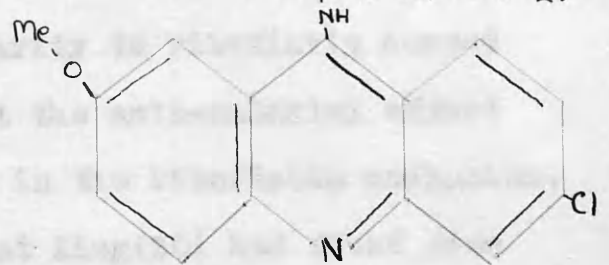
QUININE



PAMAQUIN  
Me-CH(CH<sub>2</sub>)<sub>3</sub>-N(Et)<sub>2</sub>



METHYLENE BLUE

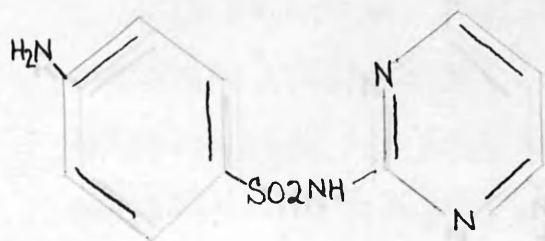


MEPACRINE

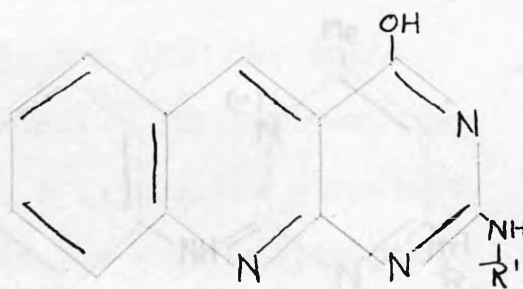
Several theories were put forward as to the mode of action of these compounds. Magidson(26), suggested that the basic side chain governed the solubility of the compound

in the body (the Pharmacological Factor), whereas the substituted acridine or quinoline nucleus was the function which governed the attack on the parasite (the Bacteriocidal Factor). Schonhoffer(27) suggested that the activity of the acridine derivatives was due to an equilibrium with the form in which the central ring was para-quinonoid.

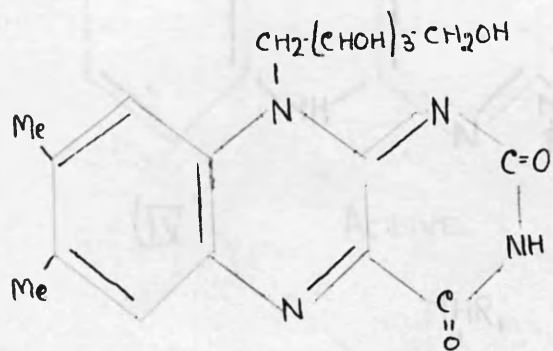
Subsequent attempts to synthesise new drugs were guided by these theories until Curd and Rose(28) departed from these ideas and obtained a completely new type of anti-malarial drug. They noted that certain sulphonamides had a slight anti-malarial activity, which, like their anti-bacterial effect, was inhibited by para-aminobenzoic acid. They thus viewed sulphonamides, e.g. Sulphadiazine, as derivatives of aniline in which the sulphonamide group acted as the Pharmacological Factor. They reasoned that less toxic anti-malarials might be obtained if a heterocyclic system of biological importance were used. Pyrimidine derivatives were thus investigated. The fact that some of these compounds bore a similarity to riboflavin caused some workers(29) to suggest that the anti-malarial effect was due to a competitive effect in the riboflavin mechanism. It should be noted, however, that King(30) had found some diaza-acridines (I) of little value and that a compound which closely resembled riboflavin had no anti-malarial effect at all (II).



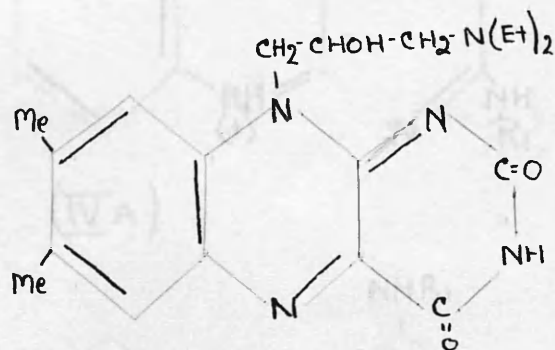
SULPHADIAZINE



(I)

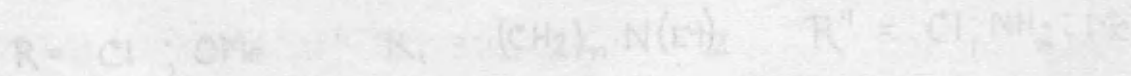


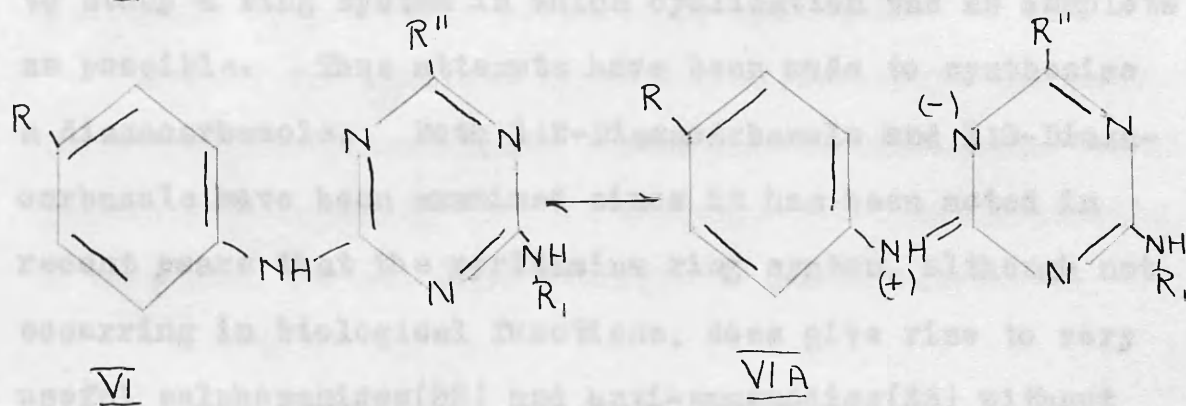
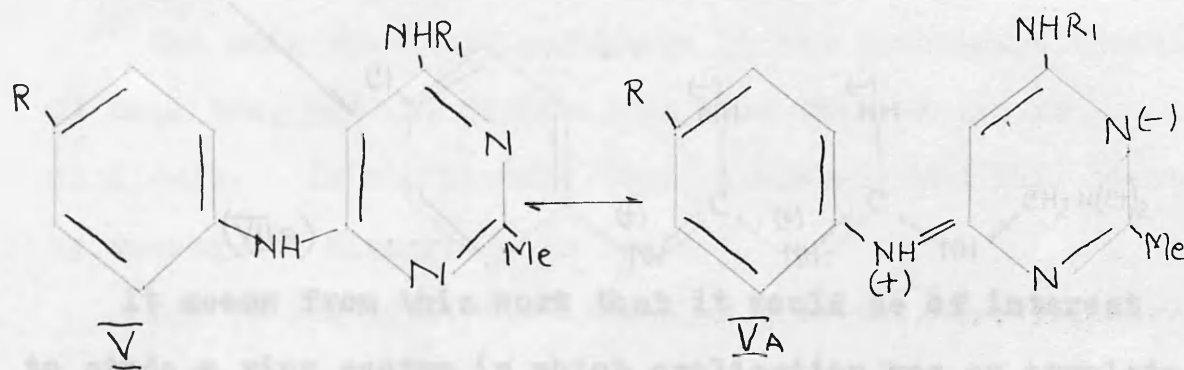
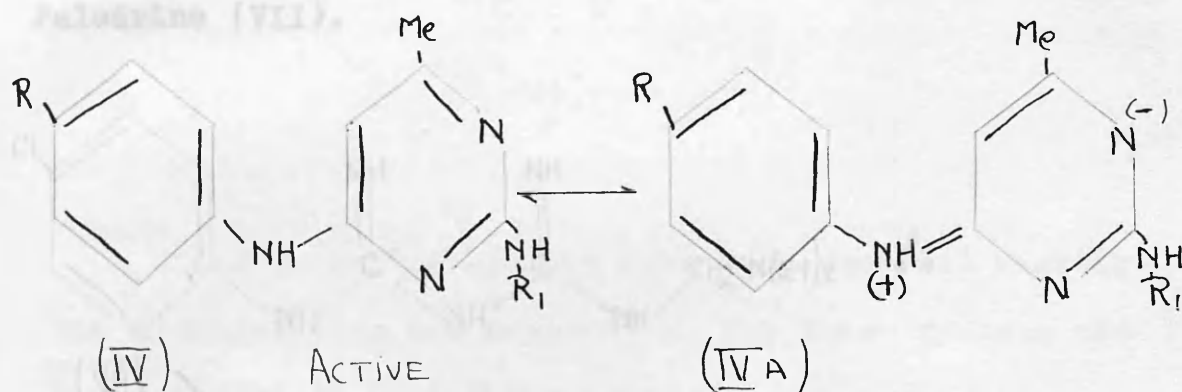
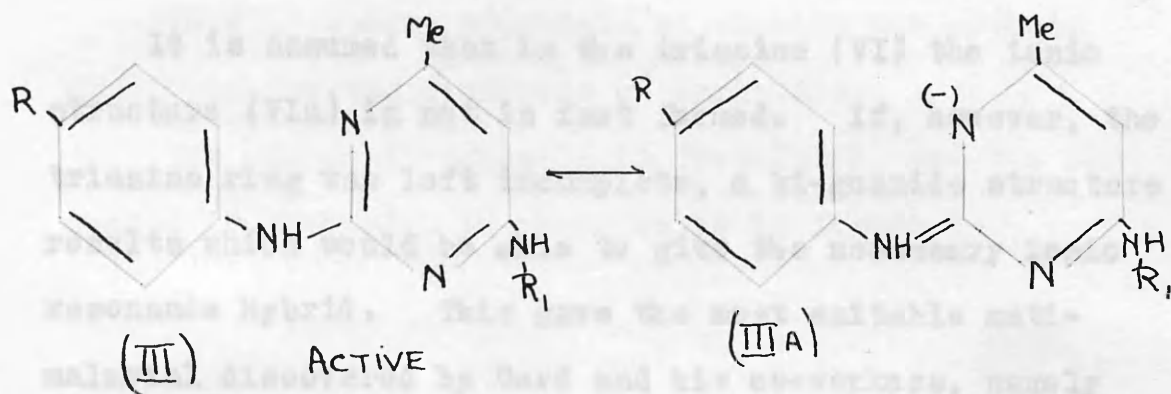
RIBOFLAVIN



(II)

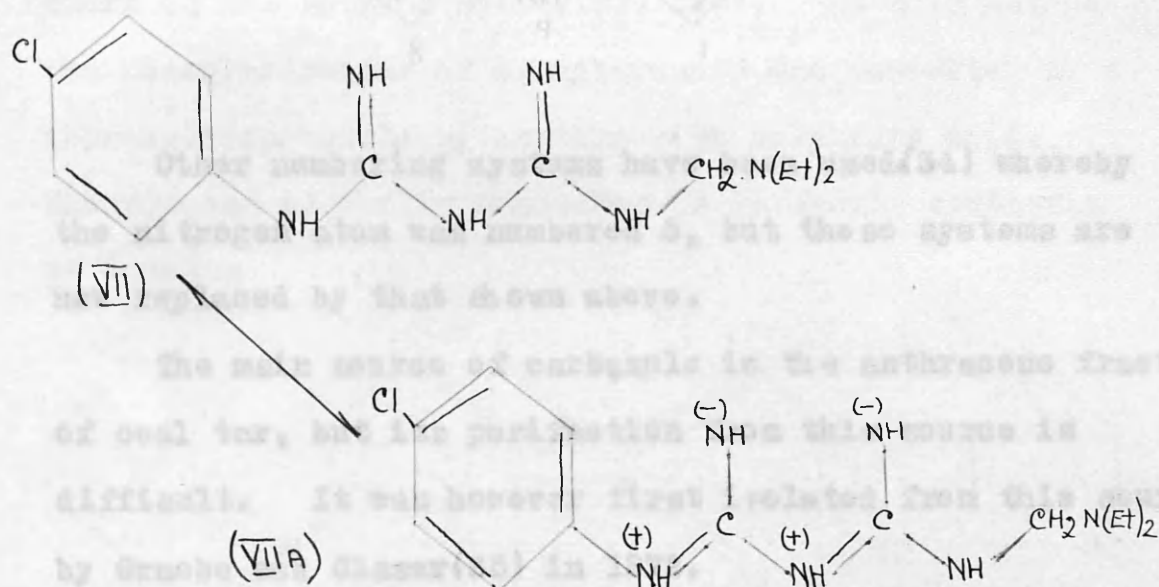
By examination of the compounds shown below, a theory was developed by Curd, Landquist and Rose(31) in which activity was related to the contributions made to the resonance hybrid by certain polarised forms, in which there was conjugation, through alternate carbon and nitrogen atoms, between the aryl groups and the terminal alkyl group R'.





$R = \text{Cl} ; \text{OMe} \quad R_1 = (\text{CH}_2)_m \cdot \text{N}(\text{Et})_2 \quad R'' = \text{Cl} ; \text{NH}_2 ; \text{Me}.$

It is assumed that in the triazine (VI) the ionic structure (VIa) is not in fact formed. If, however, the triazine ring was left incomplete, a bi-guanide structure results which would be able to give the necessary ionic resonance hybrid. This gave the most suitable anti-malarial discovered by Curd and his co-workers, namely Paludrine (VII).

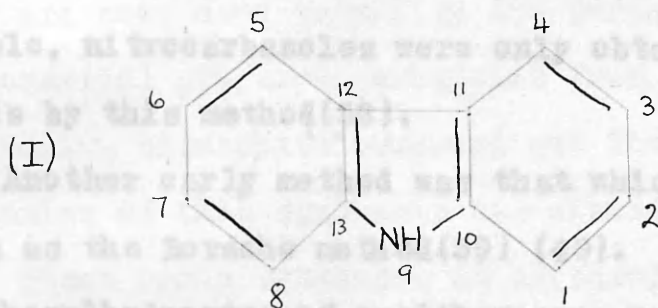


It seems from this work that it would be of interest to study a ring system in which cyclisation was as complete as possible. Thus attempts have been made to synthesise a diazacarbazole. Both 1:2-Diazacarbazole and 1:3-Diazacarbazole have been examined since it has been noted in recent years that the pyridazine ring system, although not occurring in biological functions, does give rise to very useful sulphonamides(32) and anti-spasmodics(33) without giving marked toxic effects.



Thus it became necessary to examine the methods available for the synthesis of carbazoles.

The compound carbazole is formulated, and the ring system is numbered, as shown below in figure 1.

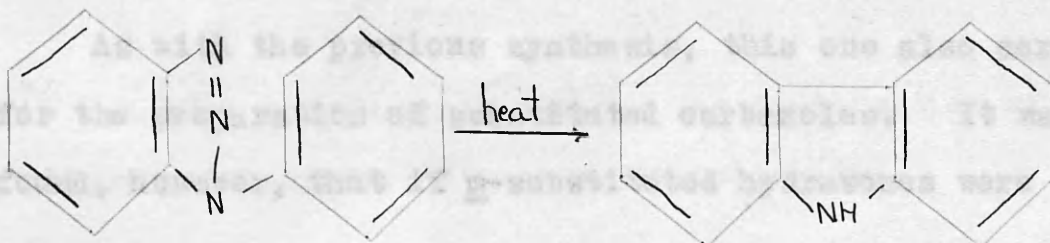


Other numbering systems have been used(34) whereby the nitrogen atom was numbered 5, but these systems are now replaced by that shown above.

The main source of carbazole is the anthracene fraction of coal tar, but its purification from this source is difficult. It was however first isolated from this source by Graebe and Glaser(35) in 1872.

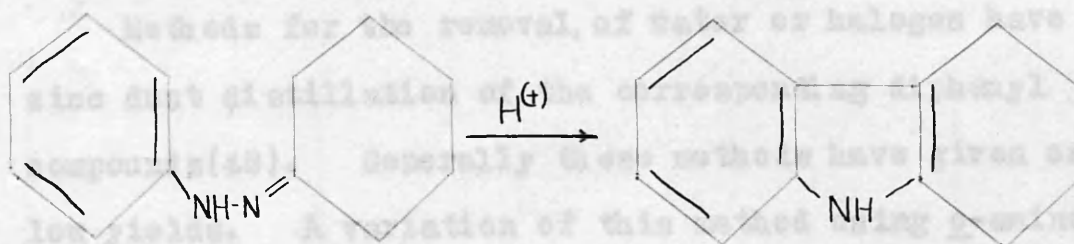
Due to its difficult isolation from this source, pure carbazole is generally prepared by synthesis.

One of the earliest syntheses of carbazole was that of Graebe and Ullmann(36). This was the diazotisation of o-aminodiphenylamine to give 1-phenyl-1:2:3-benzotriazole which, when heated, lost nitrogen to yield carbazole.



This seemed capable of wide application and by using substituted diphenylamines several substituted carbazoles were prepared(37). It was later shown that the presence of unsaturated groups inhibited this reaction. For example, nitrocarbazoles were only obtained in trace yields by this method(38).

Another early method was that which is now generally known as the Borsche method(39) (40). In this method the phenylhydrazone of cyclohexanone was converted to a tetrahydrocarbazole by heating with sulphuric acid. The process is wholly analogous to Fischer's synthesis of indole.



Any value in this method was obviated by the fact that the dehydrogenation of the tetrahydrocarbazole gave only low yields. Borsche himself, using lead dioxide obtained only low yields. Using chloranil, later workers obtained good yields in a variety of cases(41).

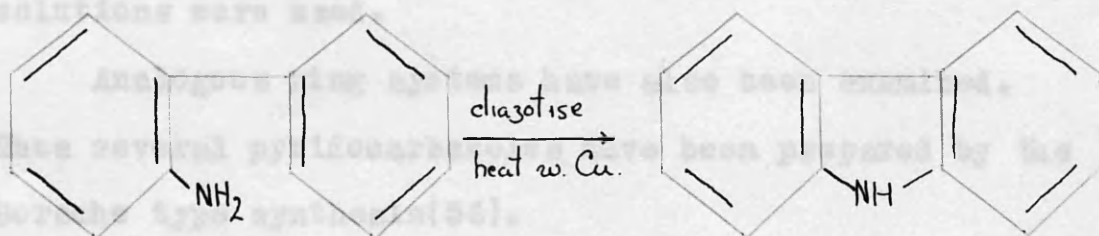
As with the previous synthesis, this one also served for the preparation of substituted carbazoles. It was found, however, that if m-substituted hydrazones were used,

then two isomeric products resulted. These were 5- and 7- substituted carbazoles as was shown by later workers (42) (43) (44).

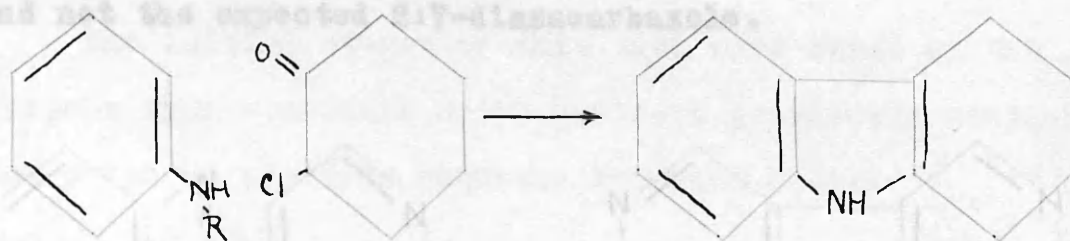
The fact that many phenols will react in the keto form has been used to modify the Borsche synthesis. Thus Bucherer(45) prepared carbazoles from suitable phenols via the sodium bisulphite compound and the hydrazone. The mechanism of this synthesis was clarified by Friedlander(46).

Other early syntheses of carbazoles were usually based on the elimination of ammonia, water or halogen from the ortho-positions of diphenyl. Thus carbazole has been prepared from 2:2'-diaminodiphenyl by prolonged treatment with sulphuric acid at 200°C (47).

Methods for the removal of water or halogen have used zinc dust distillation of the corresponding diphenyl compounds(48). Generally these methods have given only low yields. A variation of this method using o-amino-diphenyl was later used by Morgan to obtain pure carbazole (49).

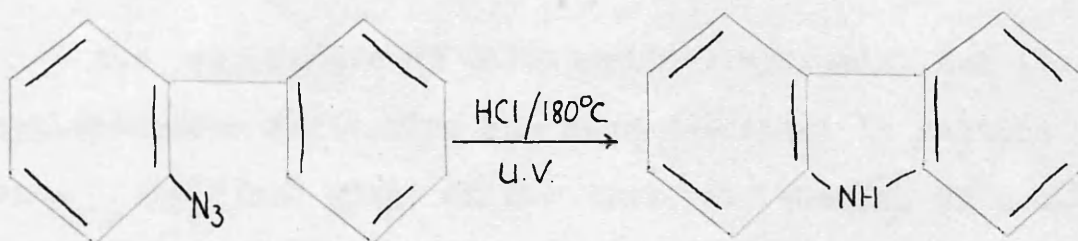


A more modern synthesis was the condensation of o-chlorocyclohexanone with aromatic amines(50).



A variation of this was the condensation of an amine with o-hydroxycyclohexanone(51) (52) (53). The mechanism of this reaction has recently been established using infra-red spectrum analysis(54).

Another modern synthesis was that involving the decomposition of suitable azides(55).

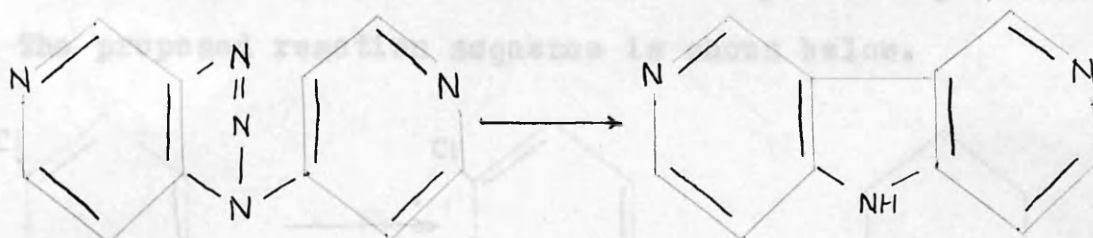


This reaction gave good yields only when very dilute solutions were used.

Analogous ring systems have also been examined. Thus several pyridocarbazoles have been prepared by the Borsche type synthesis(56).

A carbazole system containing three nitrogen atoms has also been synthesised. In decomposing 4'-pyridyl-3:4-pyridotriazole in phosphoric acid at a temperature

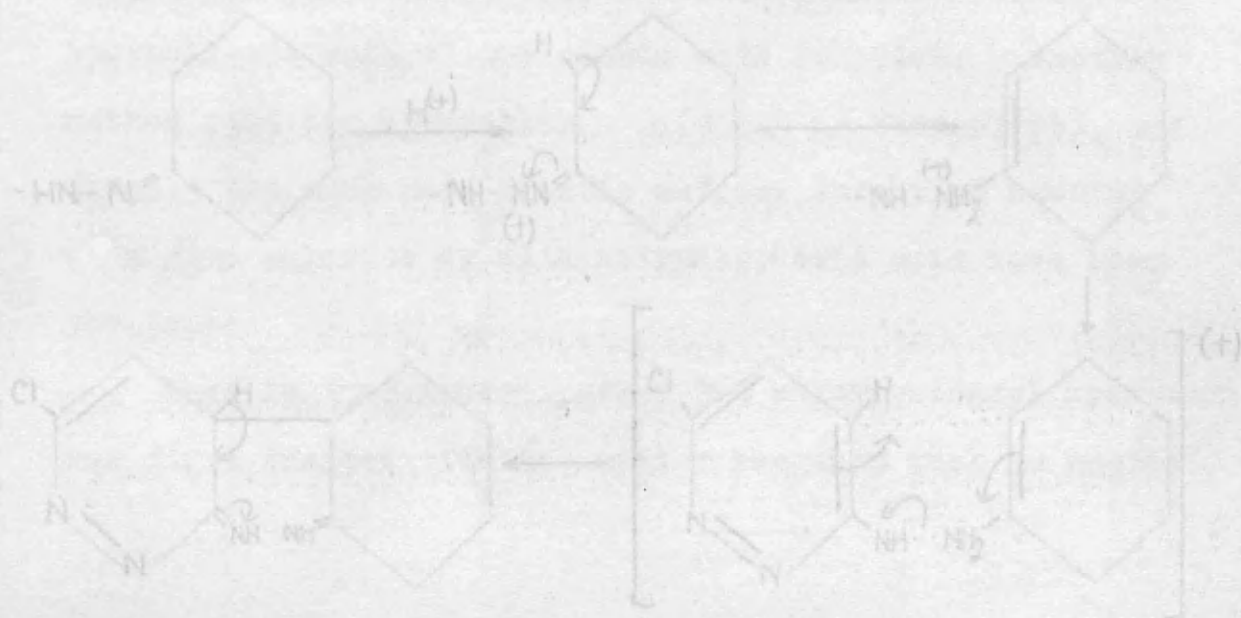
of 300°C, Koenigs and Nantka(57) obtained 3:6-diazacarbazole and not the expected 2:7-diazacarbazole.



3:6-Diazacarbazole was shown to be inert and it did not give the characteristic colour reactions of carbazoles.

The synthesis of diazacarbazoles was thus attempted using pyridazine derivatives as starting materials and the basic synthetic methods described above.

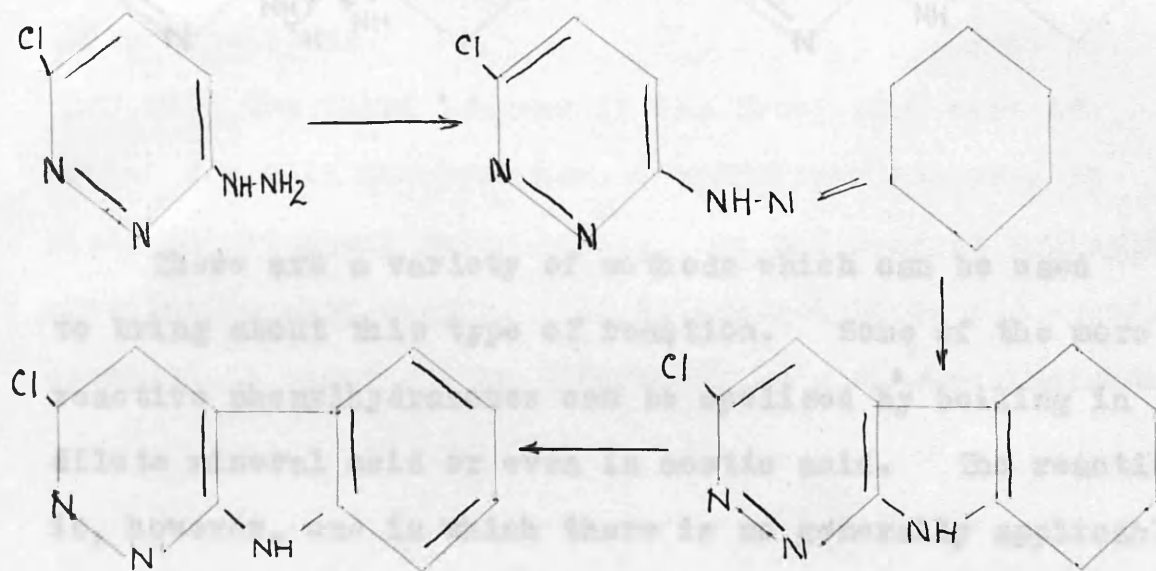
The preparation of Chloropyridazylhydrazine and its cyclohexanone derivative has been described in section one. The final stage of the synthesis should, by analogy to the recognized mechanism for the Fischer Indole synthesis, proceed as shown below.



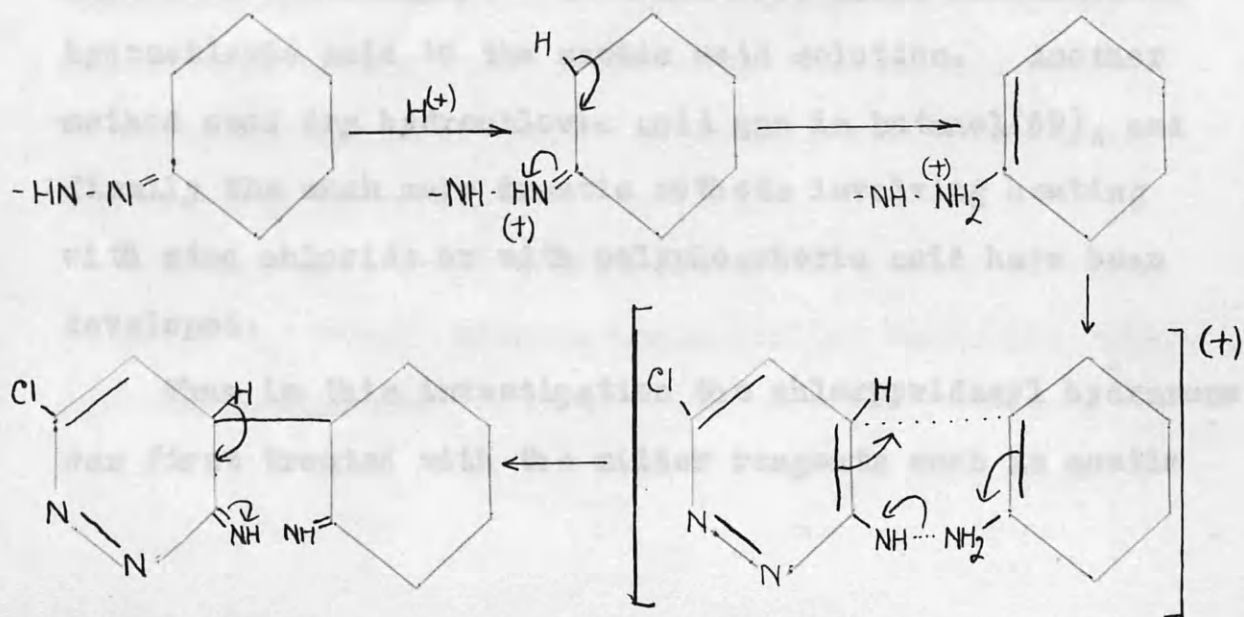


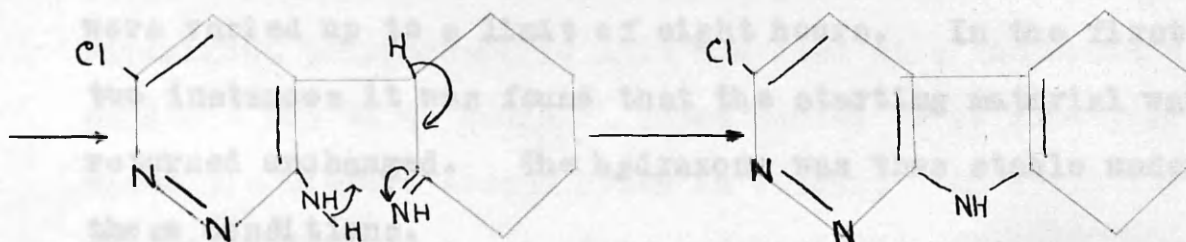
# DISCUSSION

The initial stages of this work were based on the Borsche type synthesis which has been previously mentioned. The proposed reaction sequence is shown below.



The preparation of Chlorpyridazylhydrazine and its cyclohexanone derivative has been described in section one. The final stage of the synthesis should, by analogy to the recognised mechanism for the Fischer Indole synthesis, proceed as shown below.





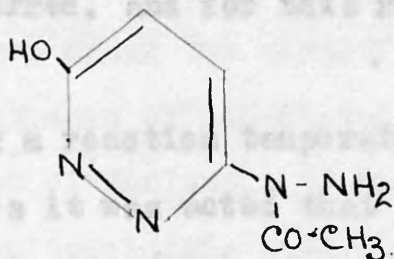
There are a variety of methods which can be used to bring about this type of reaction. Some of the more reactive phenylhydrazones can be cyclised by boiling in dilute mineral acid or even in acetic acid. The reaction is, however, one in which there is no generally applicable reagent. A reagent which gives practically theoretical yields in one case may yield hardly any cyclised product in another. Thus, over a period of years, a variety of reagents have been employed.

The main methods have evolved as more drastic reagents have become necessary. Thus Kent(58) added concentrated hydrochloric acid to the acetic acid solution. Another method used dry hydrochloric acid gas in butanol(59), and finally the much more drastic methods involving heating with zinc chloride or with polyphosphoric acid have been developed.

Thus in this investigation the chlorpyridazyl hydrazone was first treated with the milder reagents such as acetic

acid, dilute sulphuric acid and acetic acid with concentrated hydrochloric acid added. The times of heating were varied up to a limit of eight hours. In the first two instances it was found that the starting material was returned unchanged. The hydrazone was thus stable under these conditions.

With the third reagent it was found that even if boiled for only one hour marked hydrolysis occurred to yield the compound shown below. In the reagent employed acetylation also occurs. It is assumed to be a  $\beta$ -acetyl compound as suggested by Corson(60) in a similar instance.



The hydrazone was next treated with concentrated sulphuric acid in the cold. No reaction occurred and the mixture was then heated to 120°C for fifteen minutes. Starting material was again isolated in good yield from the reaction mixture.

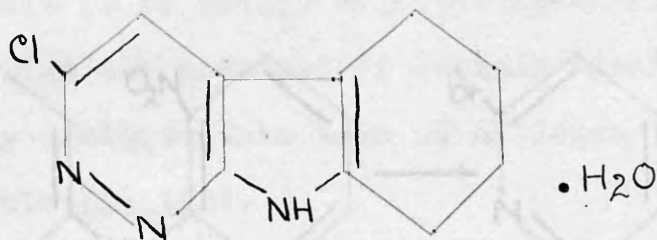
It was also found that treatment with zinc chloride at 150°C for twenty minutes again yielded unchanged chlorpyridazylhydrazone.



In a final series of attempts to cyclise this hydrazone polyphosphoric acid was used as reagent. In the first experiment polyphosphoric acid was used at a temperature of  $100^{\circ}\text{C}$  for three hours. There seemed to be some reaction since the mixture became brown in colour. On isolating the product however, starting material was obtained in almost 100% yield. The time of reaction was now varied to an upper limit of eight hours. In all cases starting material was returned unchanged from the reaction mixture.

These experiments were repeated at a temperature of  $200^{\circ}\text{C}$ , the same time variation being allowed. It was found that at this temperature rapid and drastic decomposition occurred, and for this reason no product could be isolated.

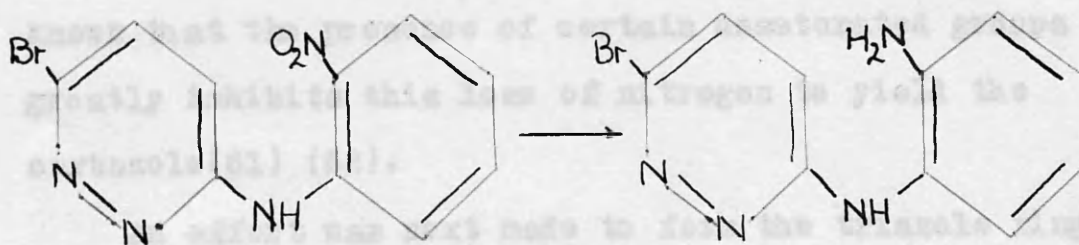
Using a reaction temperature of  $180^{\circ}\text{C}$  for a time of three hours it was noted that although considerable decomposition occurred giving a brown tarry product, a small amount of a pure product could be isolated. This product corresponded to the compound shown below.

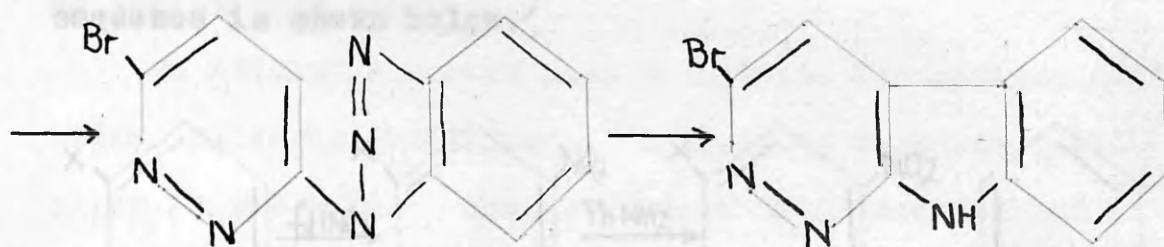


The presence of a molecule of water of crystallisation is also indicated by its unusual melting point. (softens to a glass at  $135^{\circ}\text{C}$ , melts at  $145^{\circ}\text{C}$ ). The material was converted to its picrate by boiling it with an alcoholic solution of picric acid. This gave the corresponding picrate without any water of crystallisation. The yields of both these materials were very low, due probably to the amount of decomposition which occurred. However, it was found that below this temperature no cyclisation could be induced.

Thus the preparation of 1:2-diazacarbazole by the Borsche method seems extremely difficult. There is, however, some evidence that cyclisation does occur to a small degree under the conditions of the final experiment.

A synthesis of 1:2-diazacarbazole was now attempted using a method analogous to that of Graebe and Ullmann. It has been previously mentioned that 3:6-dibromopyridazine could be condensed with o-nitraniline to give 3-bromo-6-(o-nitranilino)-pyridazine. This product was therefore used in the reaction scheme shown below.





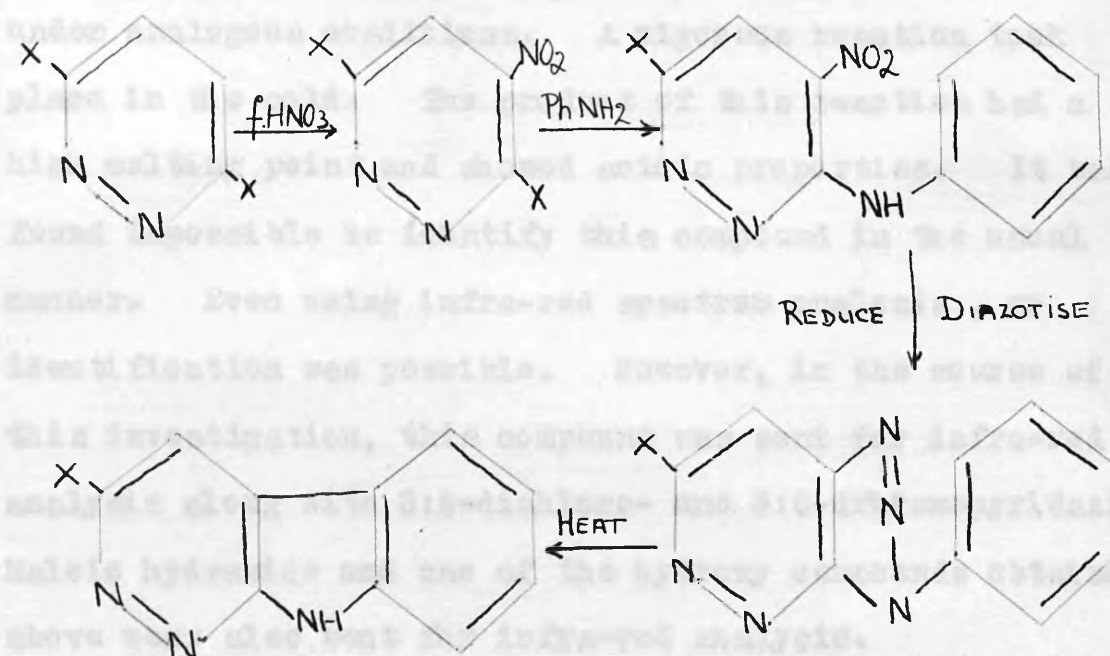
Reduction of the above mentioned nitro compound was carried out in the usual manner using Raney nickel as catalyst. The amine thus obtained was also characterised by conversion to its picrate. This amine was then diazotised using a mixture of acetic acid and potassium nitrite. On warming the diazotisation solution the triazole shown above was obtained. This compound was also characterised by conversion to its picrate.

The final stage of this synthesis depends on the tendency for triazoles to lose nitrogen on heating. The triazole was therefore <sup>heated</sup> up to a temperature of 250°C. In all cases it was found that the triazole was returned unchanged.

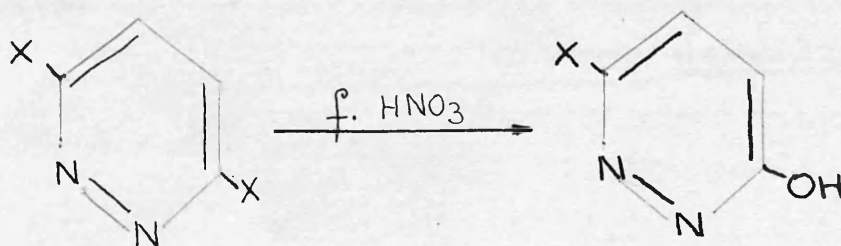
This is in accord with the known facts, since it is known that the presence of certain unsaturated groups greatly inhibits this loss of nitrogen to yield the carbazole(61) (62).

An effort was next made to form the triazole ring in a different position in the hope that the ring might

then be more easily cleaved. The proposed reaction sequence is shown below.



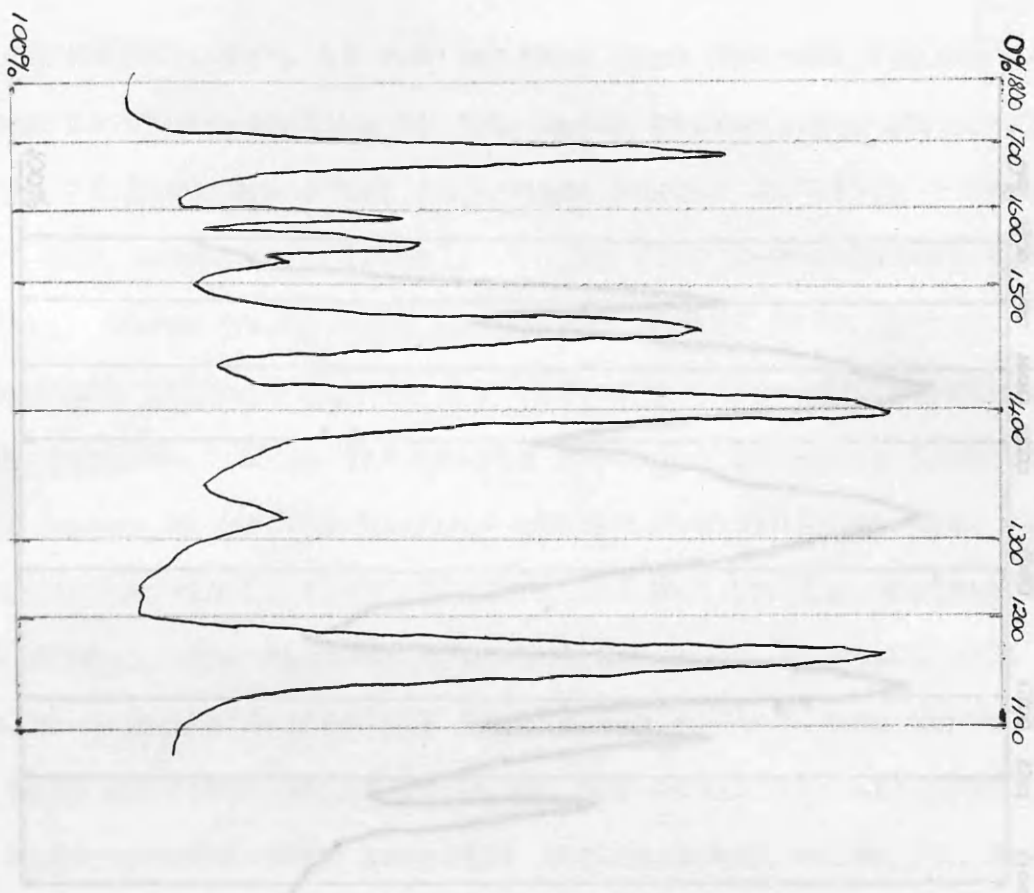
Attempts to nitrate 3:6-dichloro- and 3:6-dibromopyridazine were unsuccessful. This is probably due to the marked inactivity of the ring system towards nucleophilic reagents, due partly to the presence of the two nitrogen atoms and also to the presence of the two chlorine atoms. Even when refluxed with fuming nitric acid, no nitration was observed. There was however, an hydrolysis reaction.



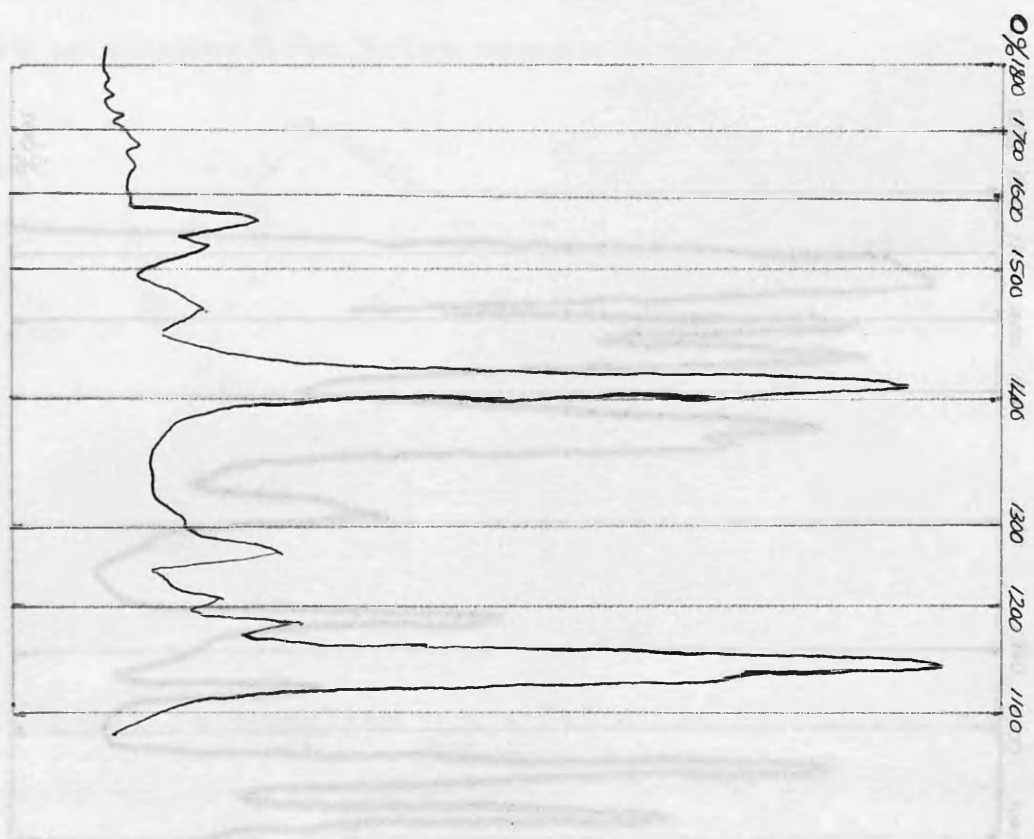
This again illustrates the marked difference in reactivity of the halogen atoms.

An attempt was next made to nitrate 3:6-pyridazinediol under analogous conditions. A vigorous reaction took place in the cold. The product of this reaction had a high melting point and showed acidic properties. It was found impossible to identify this compound in the usual manner. Even using infra-red spectrum analysis, no identification was possible. However, in the course of this investigation, this compound was sent for infra-red analysis along with 3:6-dichloro- and 3:6-dibromopyridazine. Maleic hydrazide and one of the hydroxy compounds obtained above were also sent for infra-red analysis.

The spectra of these compounds showed a series of interesting peaks. The graphs are shown overleaf. The graph of the unknown compound is not shown since there was considerable doubt about its purity. This was due to the fact that it was insoluble in all the common solvents.



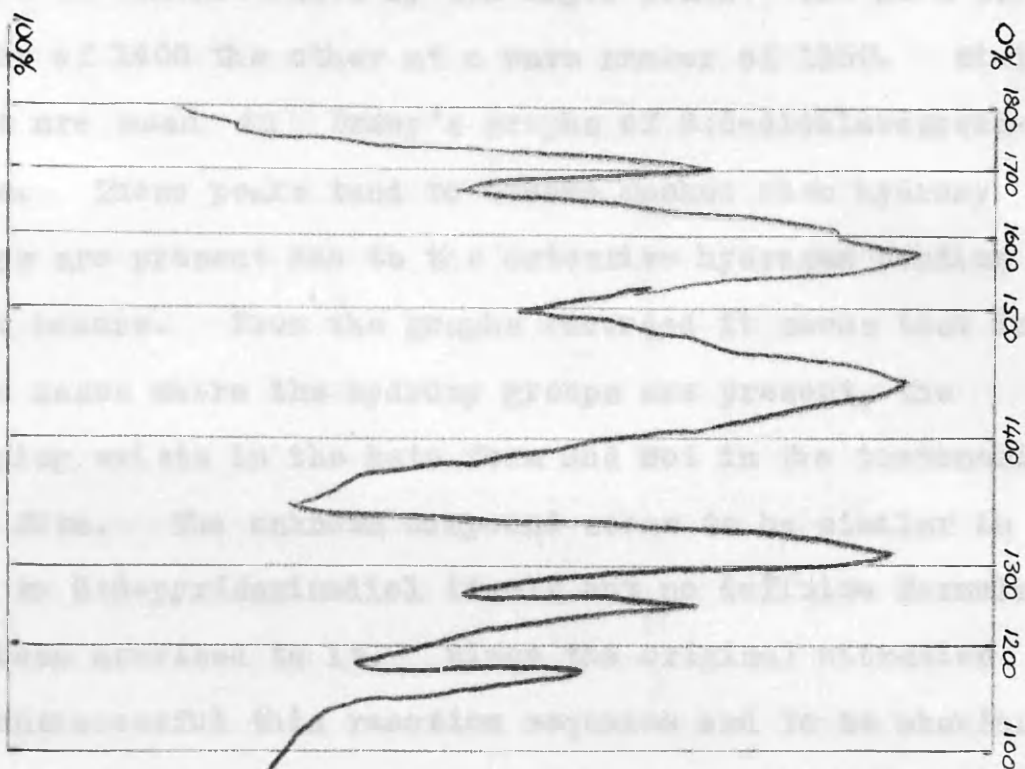
3,6-Dichloropyridazine in Nujol.



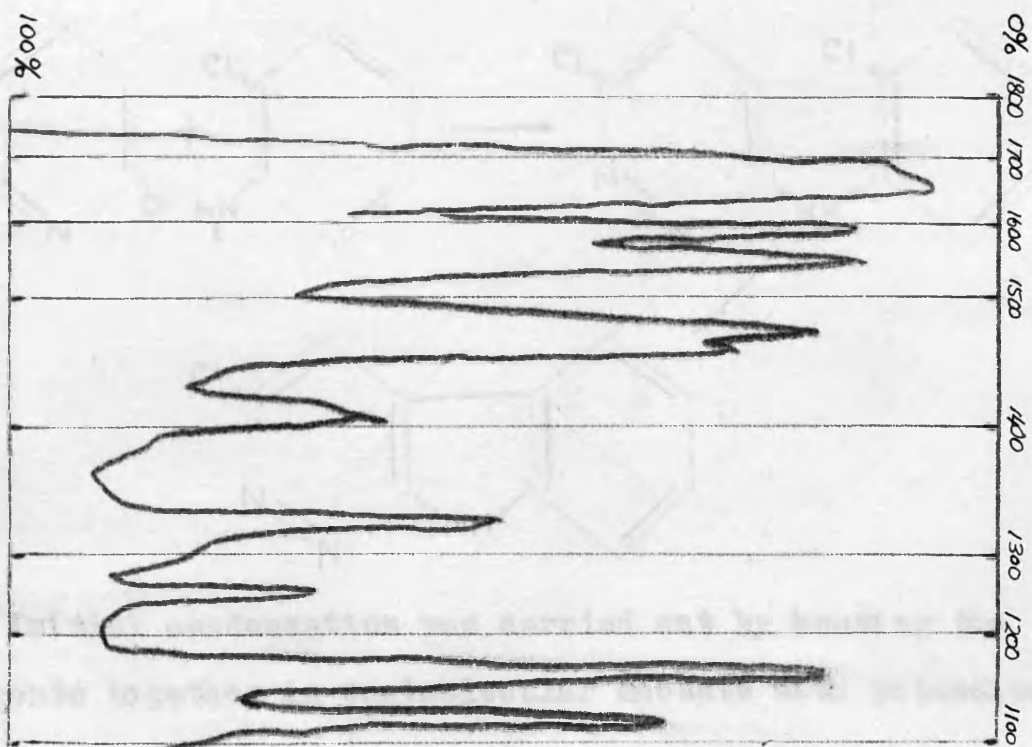
3,6-Dibromopyridazine in Chloroform.



MALEIC HYDRAZIDE IN NITROL

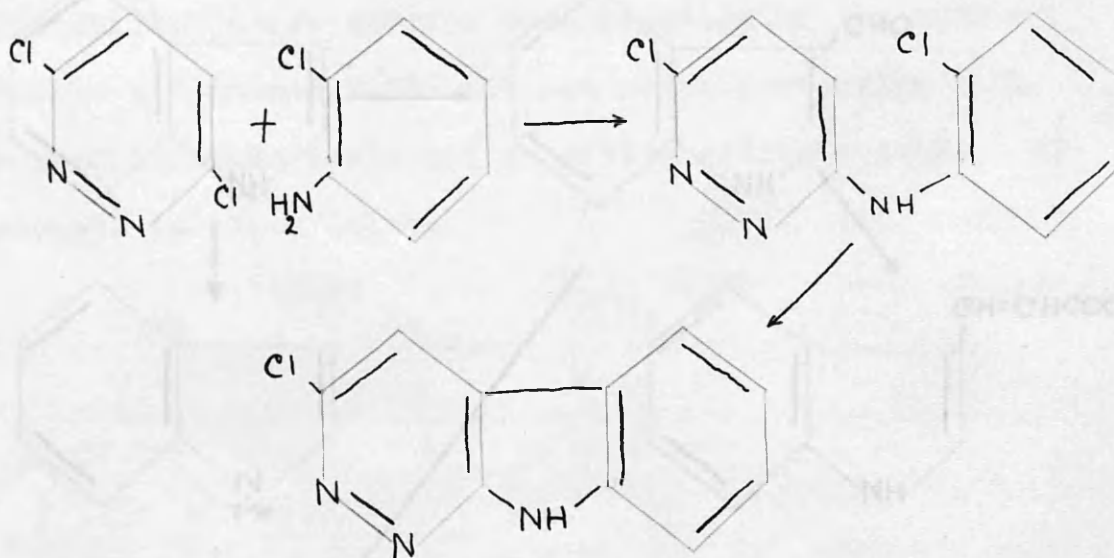


3-Bromo-6-hydroxypyridazine in Nitrol.



From this data it can be seen that the pyridazine ring system is characterised by two major peaks: one at a wave number of 1400 the other at a wave number of 1150. Similar peaks are seen in Druey's graphs of 3:6-dichloropyridazine. These peaks tend to become masked when hydroxy groups are present due to the extensive hydrogen bonding which occurs. From the graphs recorded it seems that in those cases where the hydroxy groups are present, the grouping exists in the keto form and not in the tautomeric enol form. The unknown compound seems to be similar in form to 3:6-pyridazinediol itself but no definite formula has been ascribed to it. Since the original nitration was unsuccessful this reaction sequence had to be abandoned.

In a further attempt to prepare 1:2-diazacarbazole the reaction scheme shown below was used.

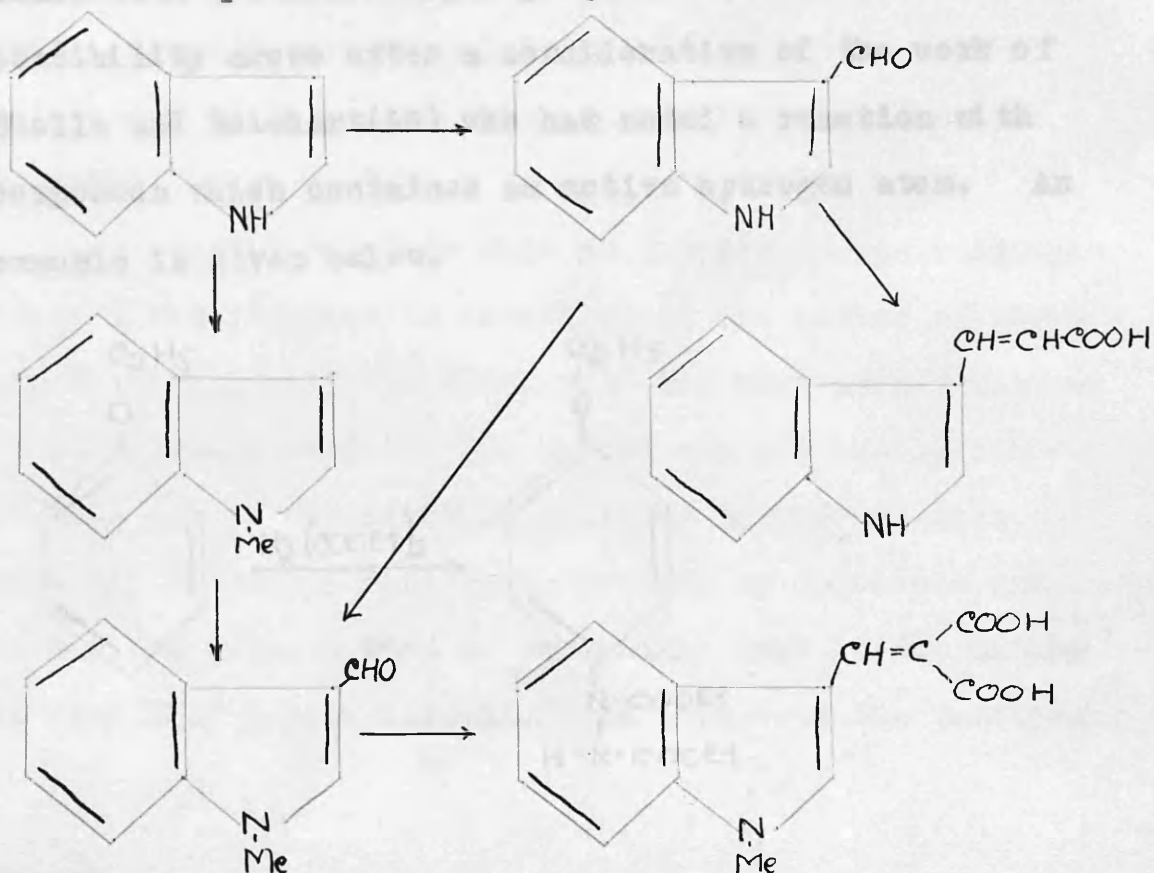


The initial condensation was carried out by heating the reagents together in equimolecular amounts with potassium

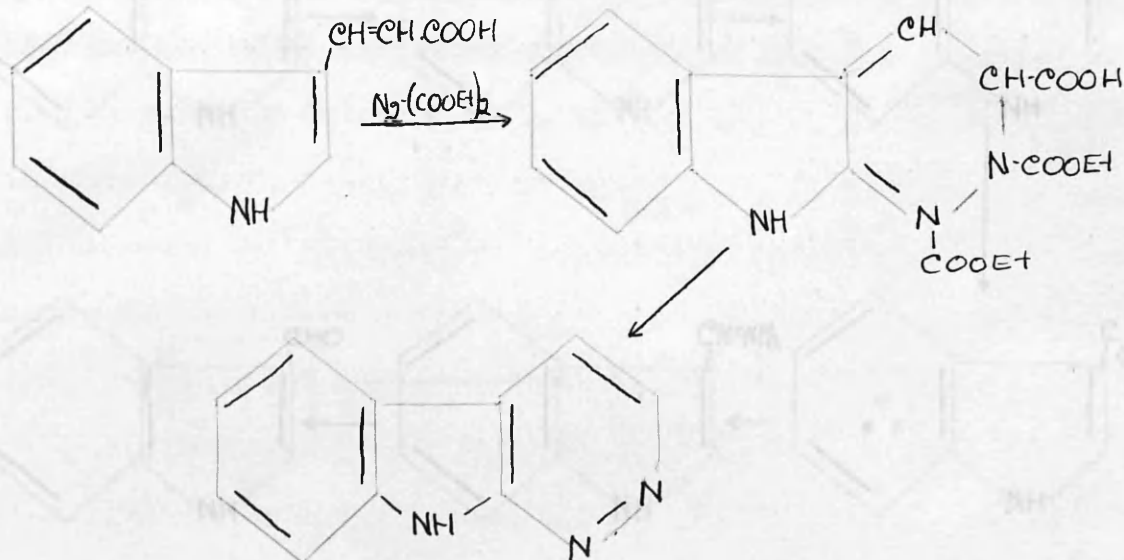


carbonate as catalyst. It was thought possible that these conditions might even bring about the final ring closure but this did not occur. The condensation product was therefore heated with aluminium chloride at  $220^{\circ}\text{C}$  for ten minutes. The starting material was returned unchanged from the reaction mixture. This cyclisation was also attempted using a zinc chloride melt. A higher reaction temperature and a longer time of reaction were used here, but again no cyclisation occurred. The starting material was again recovered unchanged from the reaction mixture.

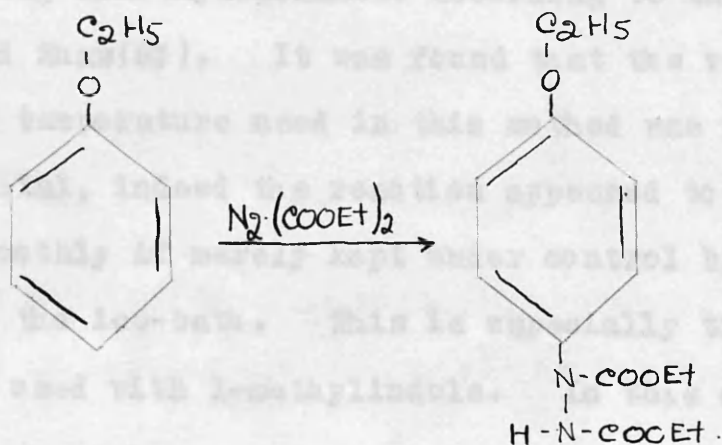
Thus due to the marked inactivity of the pyridazine ring system the usual methods of preparing a carbazole have failed. For this reason it was decided to attempt this carbazole synthesis by a more devious route. The reaction sequence is shown in part below.



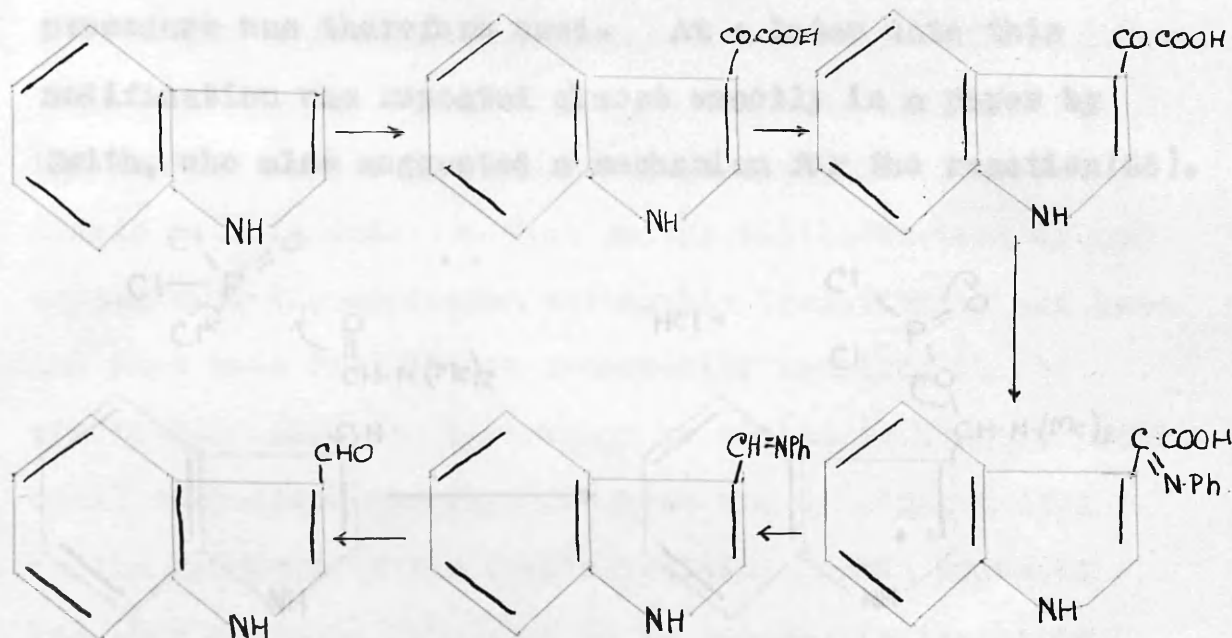
A considerable amount of work was carried out on the preparation of these basic materials. The methyl derivatives were prepared since the ultimate stages of the synthesis were as shown below.



It was thought that the ethyl azodicarboxylate might react with the free NH group of the indole nucleus. This possibility arose after a consideration of the work of Stolle and Reichart(63) who had noted a reaction with compounds which contained an active hydrogen atom. An example is given below.



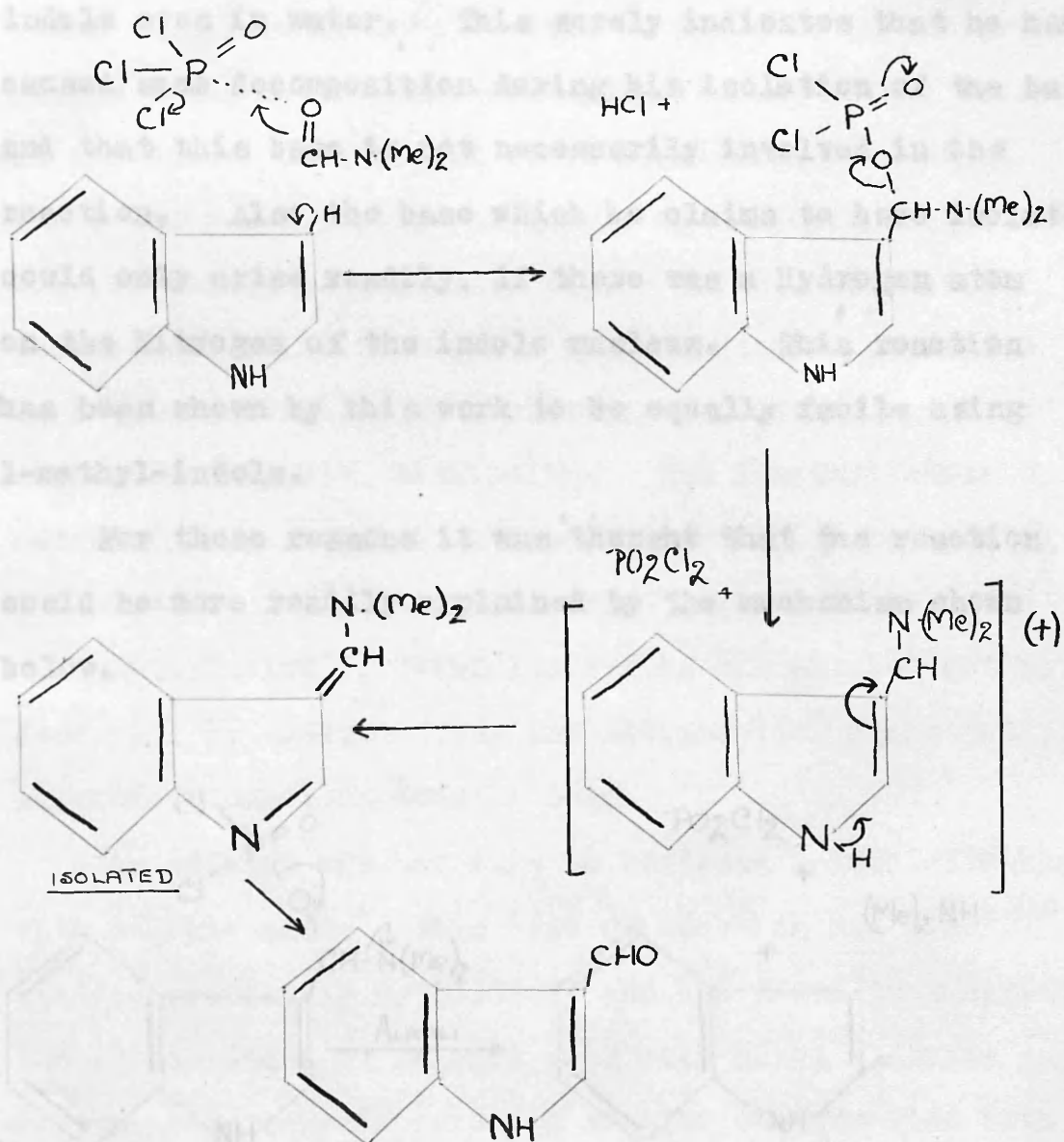
The preparation of 3-indolealdehyde was first attempted by the method of Hems(64).



However the overall yield from this method is quite low. A small amount of 3-indolealdehyde was however obtained from this synthesis and was later used as a specimen for comparison.

An attempt was then made to prepare 3-indolealdehyde using dimethylformamide according to the method of Tyson and Shaw(65). It was found that the very strict control of temperature used in this method was not wholly beneficial, indeed the reaction appeared to proceed more smoothly if merely kept under control by judicious use of the ice-bath. This is especially true if the method is used with 1-methylindole. In this case the reaction

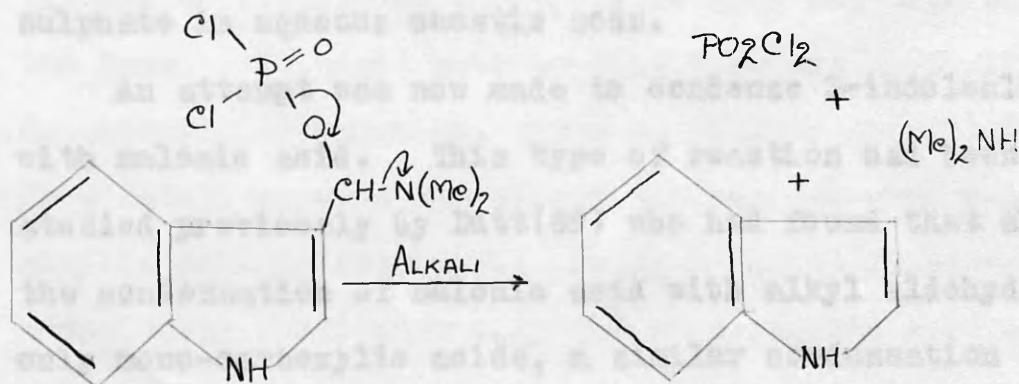
must be allowed to proceed smoothly from the start or the final stages are almost uncontrollable. A modified procedure was therefore used. At a later date this modification was repeated almost exactly in a paper by Smith, who also suggested a mechanism for the reaction(66).



On considering this mechanism however, it is difficult to understand several points in the reasoning employed

by Smith. For example he found that the product obtained by pouring the formylation mixture into water showed no spectrum of 3-formylindole until it was definitely alkaline. The base which he isolated and to which he ascribed the indolenine structure shown gave the spectrum of 3-formylindole even in water. This surely indicates that he had caused some decomposition during his isolation of the base, and that this base is not necessarily involved in the reaction. Also the base which he claims to have isolated could only arise readily, if there was a Hydrogen atom on the Nitrogen of the indole nucleus. This reaction has been shown by this work to be equally facile using 1-methyl-indole.

For these reasons it was thought that the reaction could be more readily explained by the mechanism shown below.



Using this modified procedure a quantity of 3-indole-aldehyde was prepared.

The methylation of indole was initially carried out using the method of Potts and Saxton(67). This procedure involved the use of sodium in liquid ammonia. It was found that 1-methylindole could be prepared in comparable yields using solid potassium hydroxide and methyl iodide in acetone. This result is of considerable interest since the n-methylation of indole by a simple method has not previously been carried out. Normal methylation techniques, other than those using sodium or potassium in liquid ammonia, give a mixture of products which is separated only with difficulty. The 1-methylindole thus obtained was converted to 1-methyl-3-indole-aldehyde by the modified formylation procedure mentioned above.

II- Methylation of 3-indolealdehyde was carried out as described by Wieland, Konz and Mittasch(68) using methyl sulphate in aqueous caustic soda.

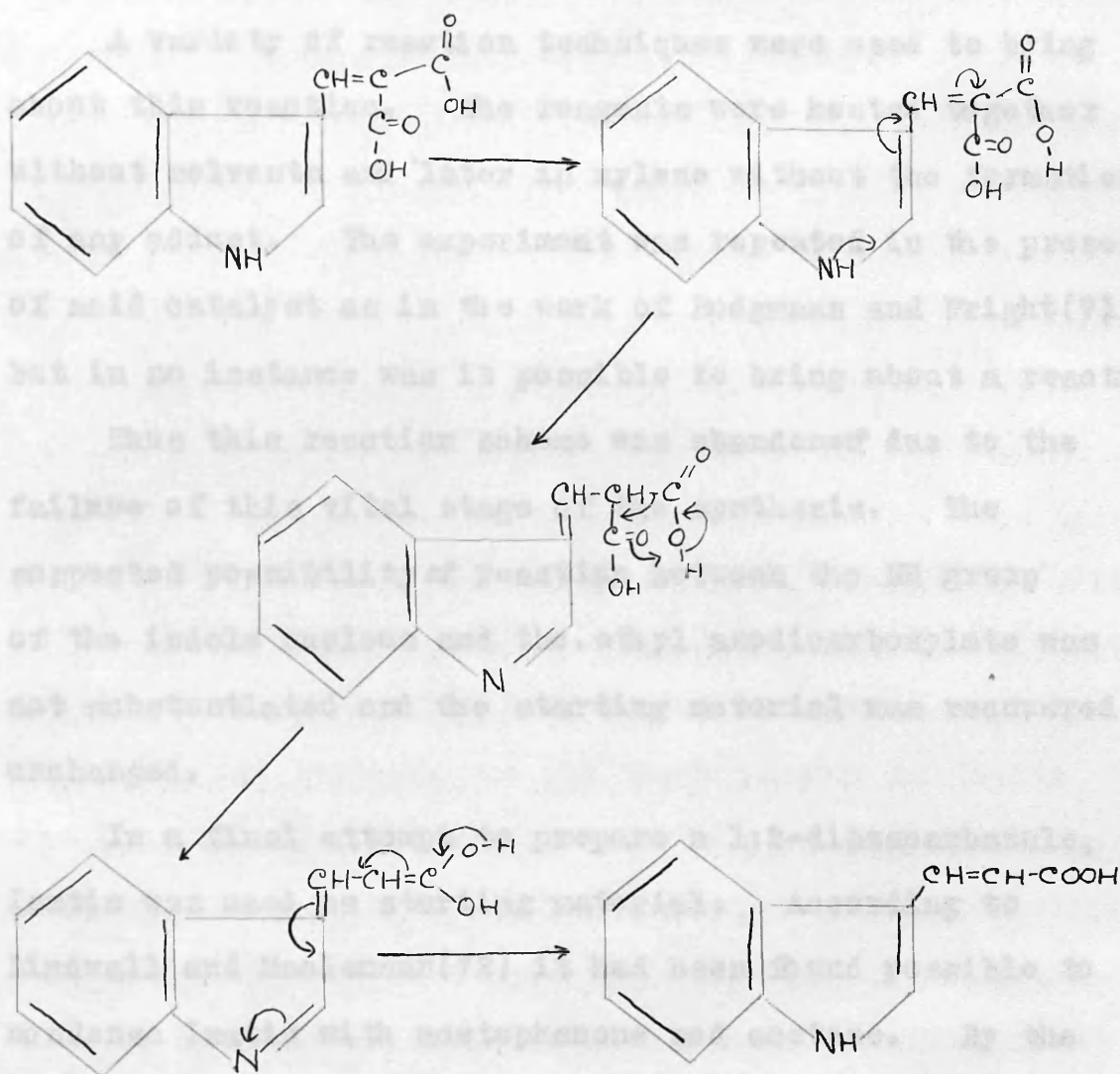
An attempt was now made to condense 3-indolealdehyde with malonic acid. This type of reaction had been studied previously by Dutt(69) who had found that although the condensation of malonic acid with alkyl aldehyde gave only mono-carboxylic acids, a similar condensation with aryl aldehyde generally yielded the dicarboxylic acid. He did however, note that decarboxylation occurred very

readily in pyridine especially if the reaction was heated. Pandya and Pandya(70) using a similar method but heating the reaction were able to prepare a variety of mono-carboxylic acids from malonic acid. An example of their work is given in the Journal of Chemical Education, whereby they prepared cinnamic acid from benzaldehyde and malonic acid.

The method used by Dutt required a slow reaction at room temperature for sixty hours. This method yielded 3-indolylacrylic acid. This method was modified in the following manner. The reagents were mixed and warmed to forty degrees for ten minutes and then allowed to cool and stand at room temperature for three hours. In this way 3-indolylacrylic acid was obtained. It is interesting to note that initially a white micro-crystalline solid is obtained which melts at a much lower temperature than 3-indolylacrylic acid and evolves carbon dioxide at this lower temperature. It was thought that this might analyse for the corresponding dicarboxylic acid but this was not the case. It might well be that this was partially decarboxylated material, since on further recrystallisation from methyl cyanide the colour darkens and pure 3-indolylacrylic acid is obtained. Using 1-methyl-3-indolealdehyde under these conditions only the dicarboxylic acid was obtained. Even after prolonged crystallisation the two carboxyl groups were unaffected. Thus the methyl group attached to the nitrogen seems to stabilise the malonic acid adduct so that subsequent decarboxylation does not occur.



The exact nature of this stabilisation cannot be verified but it is suggested that the mechanism is that shown below.



Thus in the case of the <sup>N</sup>-methylated compound, wherein no preliminary hydrogen ion migration could occur, any similar decarboxylation mechanism would give rise to the unfavourable allene structure and it is thus assumed that this is the reason for the stabilisation effect.

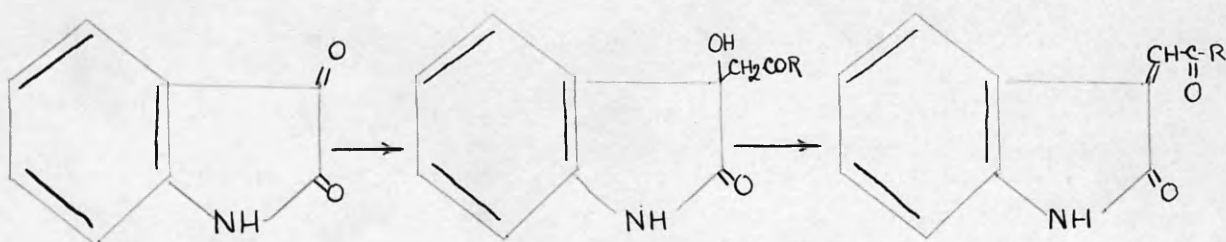


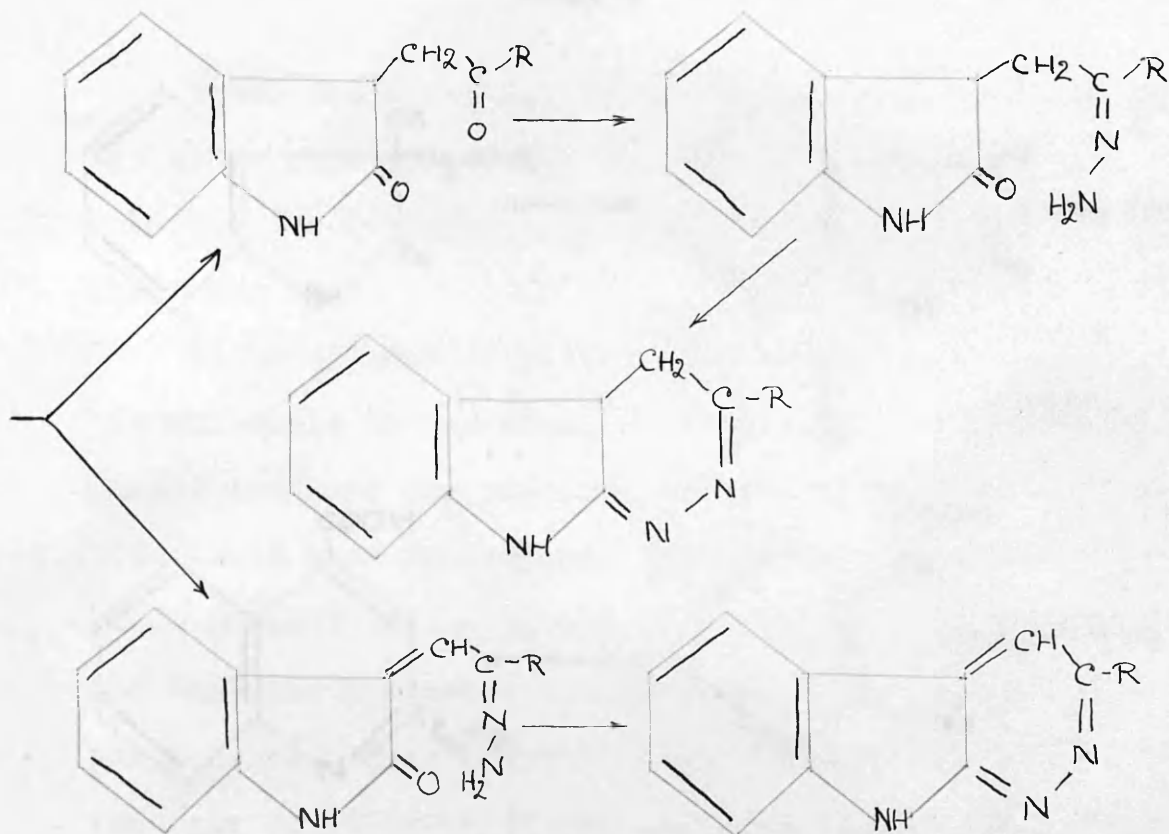
Both of these compounds possess a potential diene system which might undergo a Diels-Alder reaction. For this reason attempts were made to react these materials with the dienophile, ethyl azodicarboxylate.

A variety of reaction techniques were used to bring about this reaction. The reagents were heated together without solvents and later in xylene without the formation of any adduct. The experiment was repeated in the presence of acid catalyst as in the work of Rodgmann and Wright(71), but in no instance was it possible to bring about a reaction.

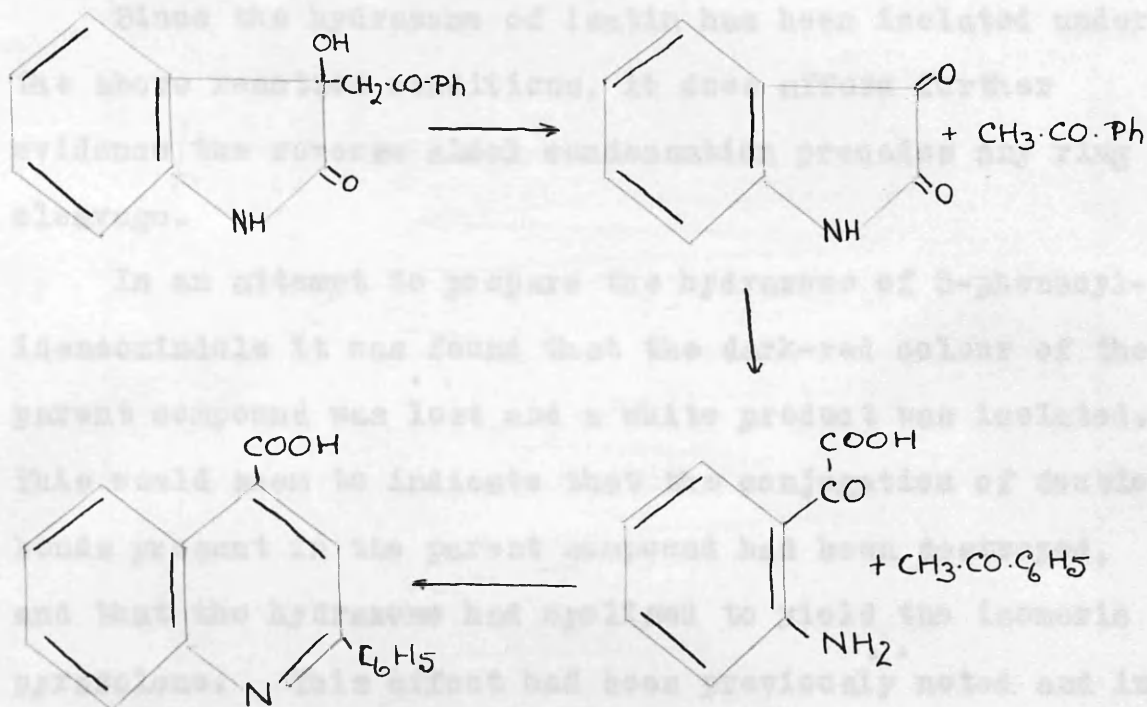
Thus this reaction scheme was abandoned due to the failure of this vital stage of the synthesis. The suspected possibility of reaction between the NH group of the indole nucleus and the ethyl azodicarboxylate was not substantiated and the starting material was recovered unchanged.

In a final attempt to prepare a 1:2-diazacarbazole, Isatin was used as starting material. According to Lindwall and MacLennan(72) it had been found possible to condense Isatin with acetophenone and acetone. By the reaction sequence shown below these adducts might be made to yield the phenyl and methyl diazacarbazoles.

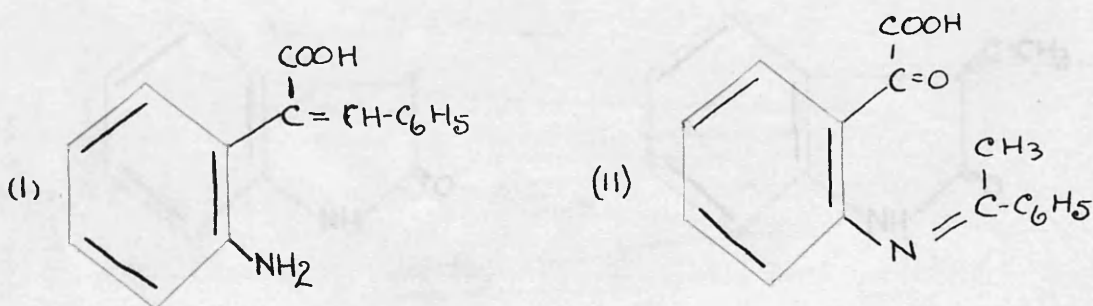




In the course of this work several interesting facts arose. It was found that 3-hydroxy-3-phenacyloxindole on treatment with hydrazine hydrate was decomposed rapidly to Isatin and acetophenone and the hydrazone of Isatin was isolated from the reaction. This is further indication of the ease with which 3-hydroxy-3-phenacyloxindole is decomposed, as was suggested by Lindwall and Maclellan (72) in their interpretation of the Fittzinger mechanism whereby 3-hydroxy-3-phenacyloxindole is converted to cinchophen by the use of caustic soda in ethanol.



These workers show that compound (1) below is unlikely as the penultimate step, since simple hydrolytic cleavage of 3-phenacylideneoxindole should yield the same compound if this were true. In actual fact this is not the case and it thus seems that the penultimate step in the formation of cinchophen is the formation of a simple amide linkage to yield compound (2) below.

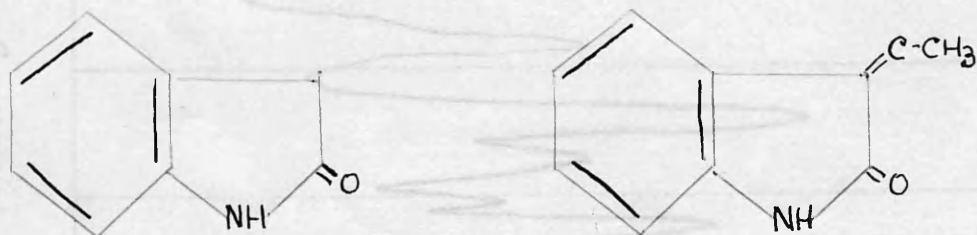


Since the hydrazone of isatin has been isolated under the above reaction conditions, it does afford further evidence the reverse aldol condensation precedes any ring cleavage.

In an attempt to prepare the hydrazone of 3-phenacylideneoxindole it was found that the dark-red colour of the parent compound was lost and a white product was isolated. This would seem to indicate that the conjugation of double bonds present in the parent compound had been destroyed, and that the hydrazone had cyclised to yield the isomeric pyrazolene. This effect had been previously noted and in the case of pulegone it had been proved that this occurs, by synthesising the pyrazolene by an unambiguous route.

The loss of colour and hence conjugation in the compounds examined above would largely indicate the formation of the pyrazolene structure. This was further proved by a consideration of the infra-red spectra of the compounds.

The spectrum obtained from this compound was compared with the spectra of the compounds shown below.

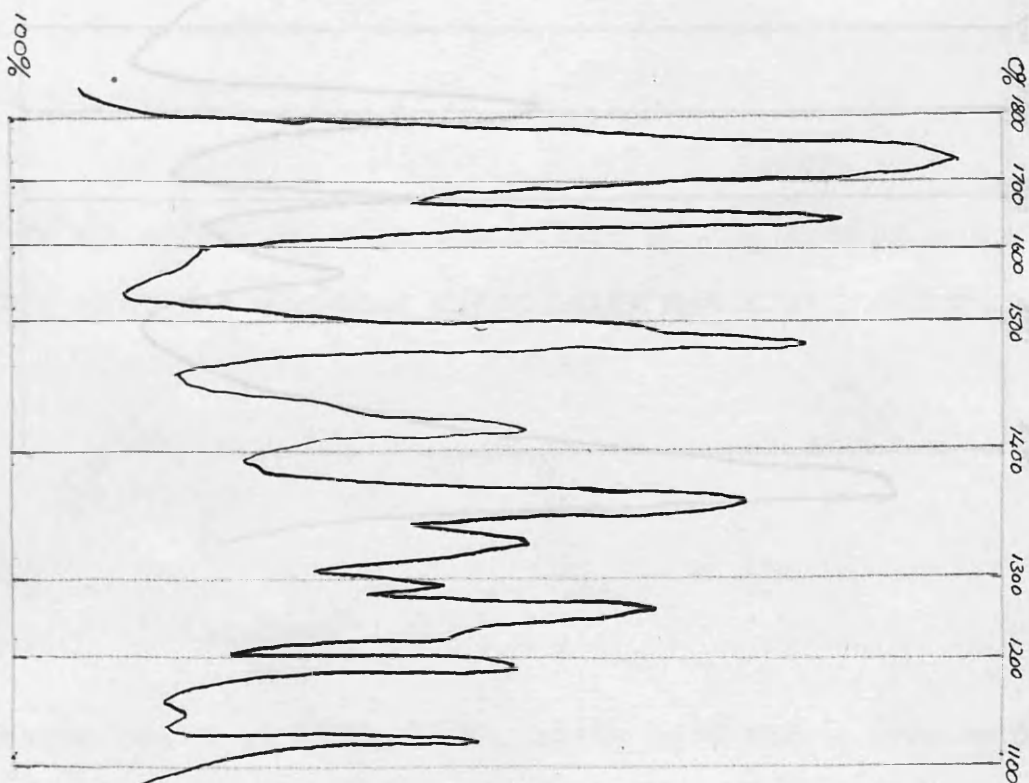


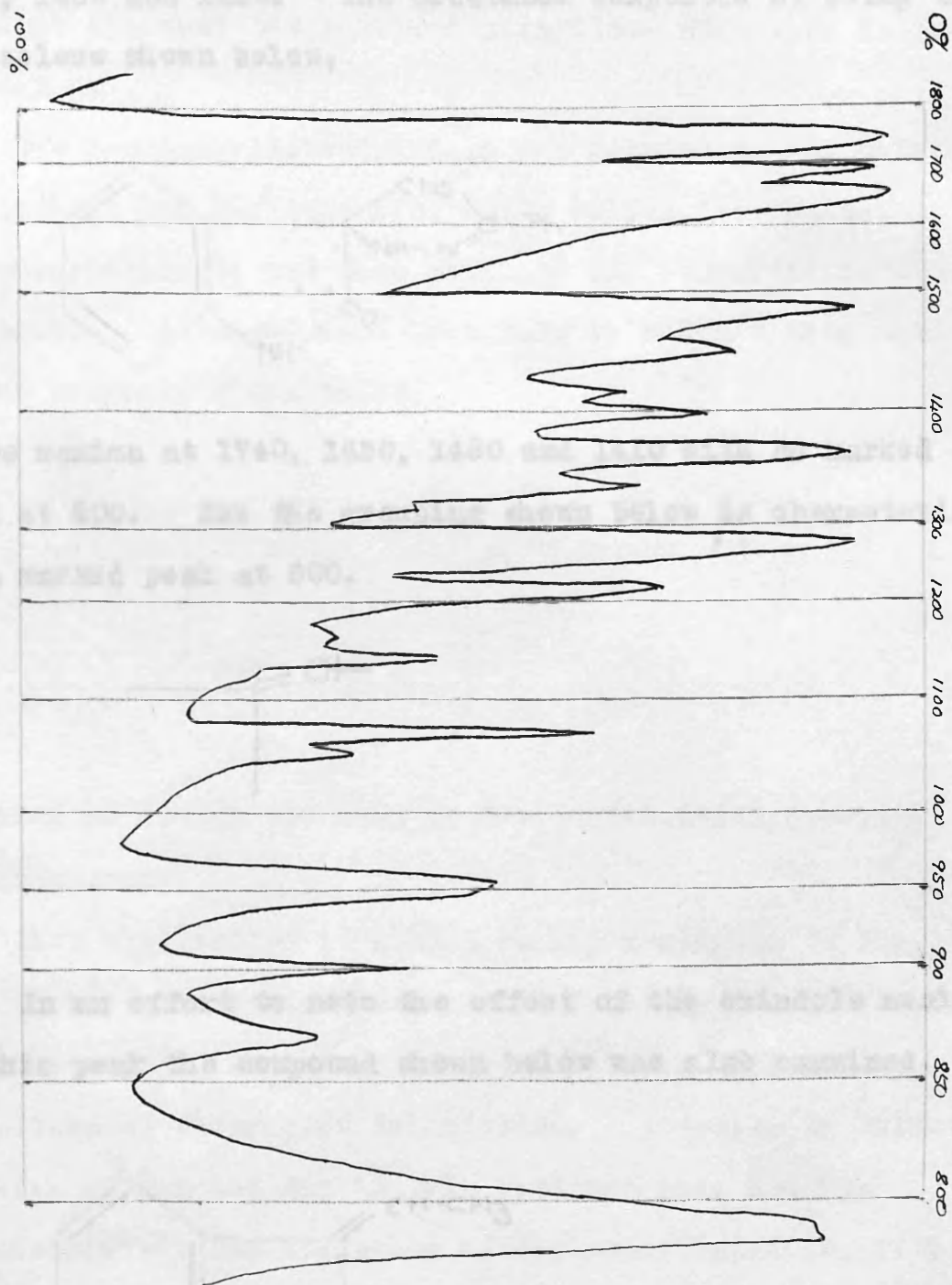
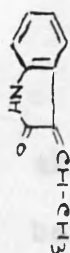
The spectra show a considerable degree of similarity, the graphs are recorded overleaf.

PYRAZOLENE IN NITOL



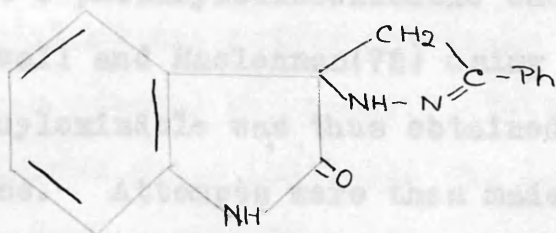
OXINDOLE IN CHLOROFORM



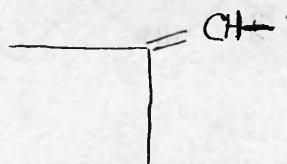




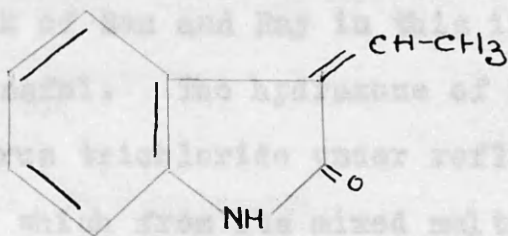
Oxindole itself shows maxima at wave numbers of 1740, 1640, 1480 and 1420. The substance suspected of being the pyrazolene shown below,



shows maxima at 1740, 1650, 1480 and 1410 with no marked band at 800. Now the grouping shown below is characterised by a marked peak at 800.



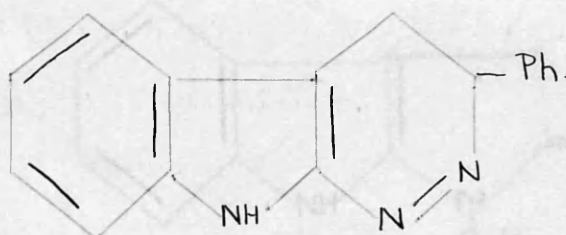
In an effort to note the effect of the oxindole nucleus on this peak the compound shown below was also examined.



It showed peaks at 1740, 1700, 1640, 1490 and a very marked peak at 782. This further indicates that the group in

question is absent from the hydrazone of 3-phenacylidene-oxindole and that the ascribed pyrazolene structure is the correct one.

The 3-phenacylidineoxindole was reduced by the method of Lindwall and Maclellan(72) using sodium dithionite. 3-Phenacyloxindole was thus obtained and converted to its hydrazone. Attempts were then made to convert this material to the compound shown below,

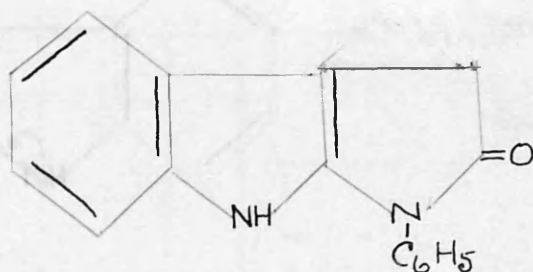


to which we assign the name of 3-phenyl-3:4-dihydro-1:2-diazacarbazole.

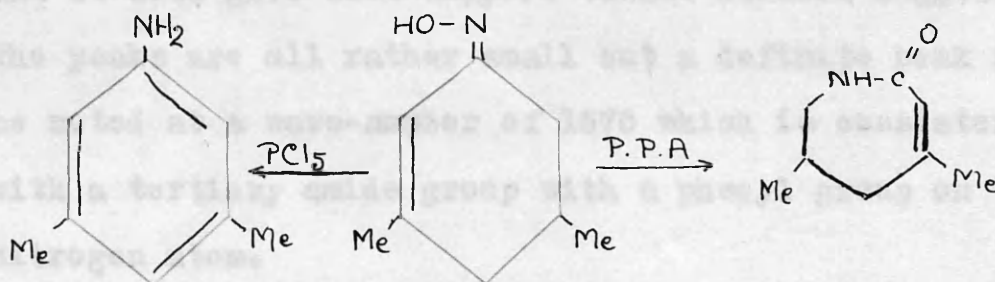
This cyclisation is almost wholly analogous to the work on the amidine synthesis carried out by Sen and Ray(73) who successfully condensed an amine with an acylamine by the action of phosphorus trichloride. Attempts to follow the work of Sen and Ray in this instance were however unsuccessful. The hydrazone of 3-phenacyloxindole, with phosphorus trichloride under reflux, gave a hydrolysis product which from its mixed melting point seemed to be 3-phenacyloxindole.



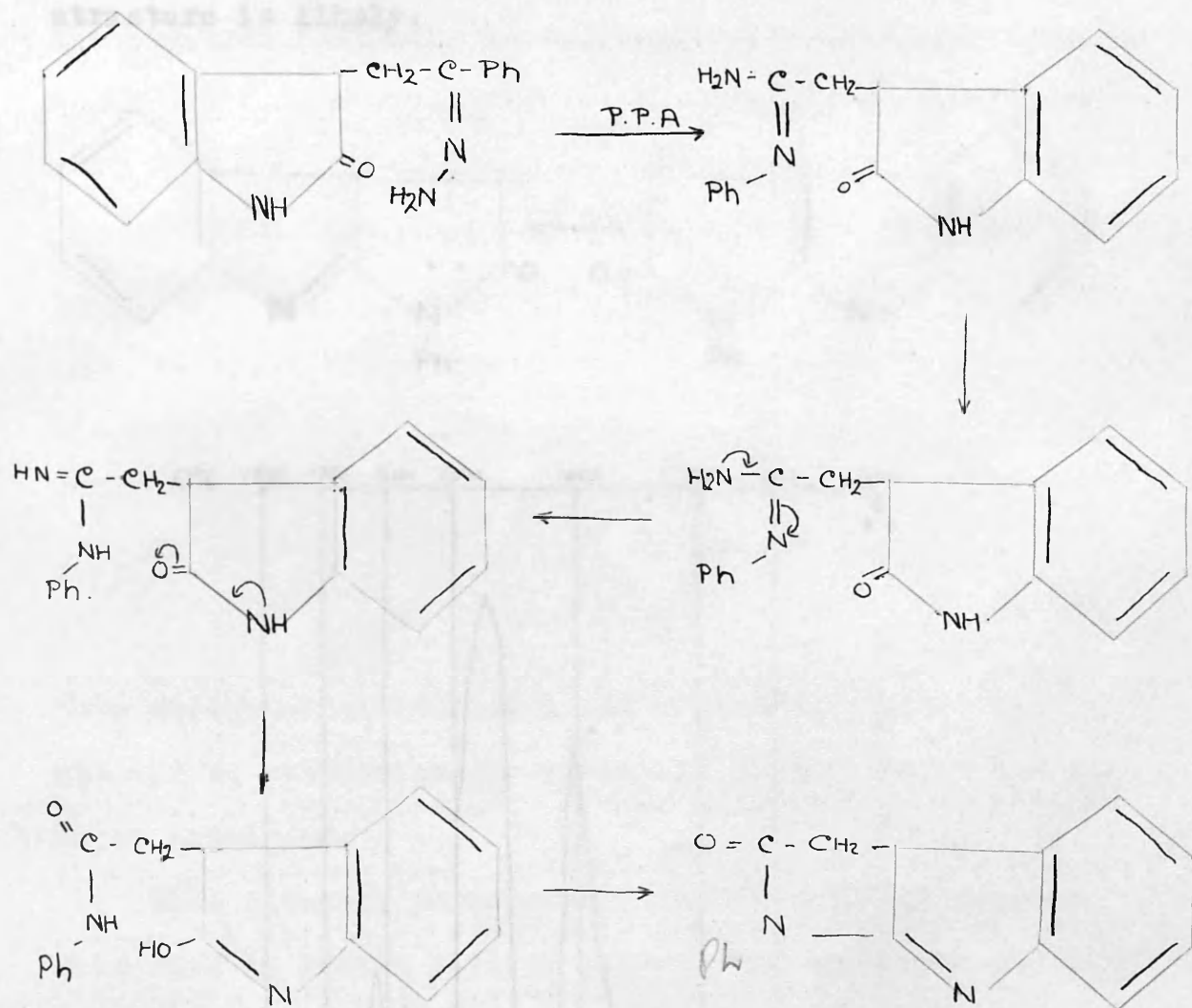
Attempts to bring about the cyclisation by means of polyphosphoric acid at  $100^{\circ}\text{C}$  were also unsuccessful. A product was isolated, but its analysis figures did not correspond to those of the above carbazole. The compound thus obtained was rather insoluble but was finally crystallised from ethanol and water. This product on analysis gave figures which indicated the loss of an atom of nitrogen. The compound seemed to be the one shown below.



It is suggested that the change occurs by way of an unusual Beckmann rearrangement. The use of polyphosphoric acid in this reaction had been described previously by Horning and Stromberg(74). In their work they showed that polyphosphoric acid could be used to give amides from aldoximes and that in cyclohexenone oximes the Wolff aromatisation could be avoided and the amide produced.

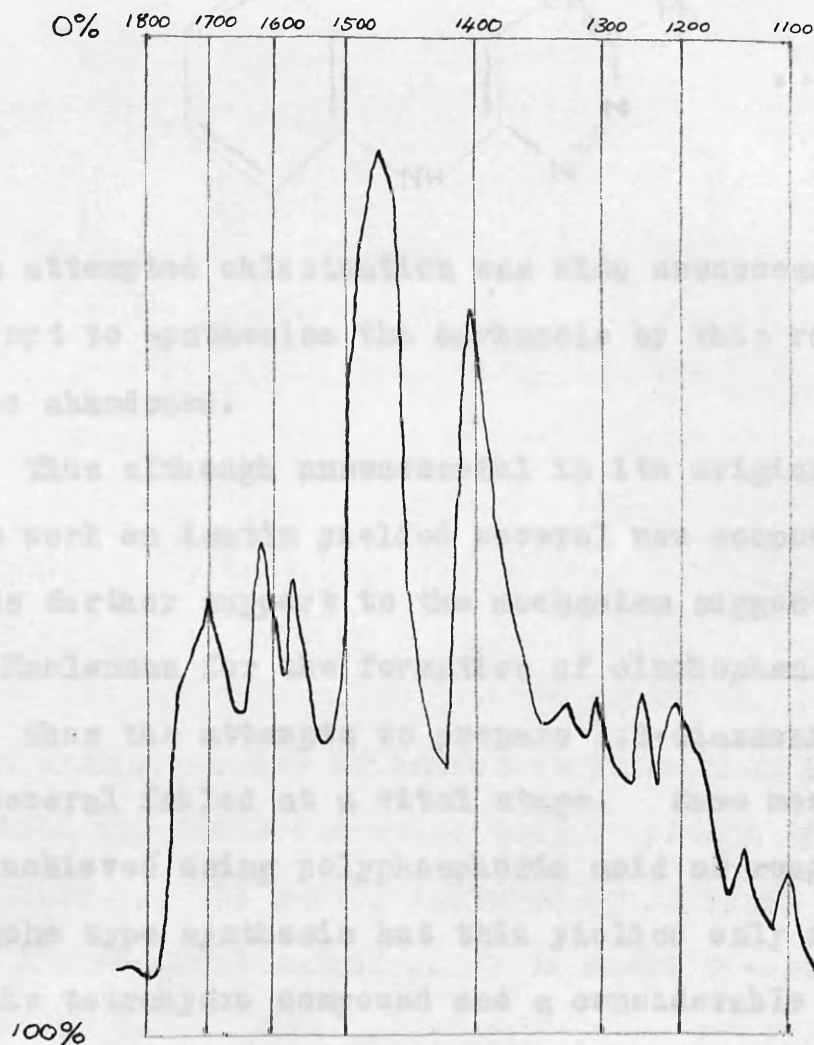
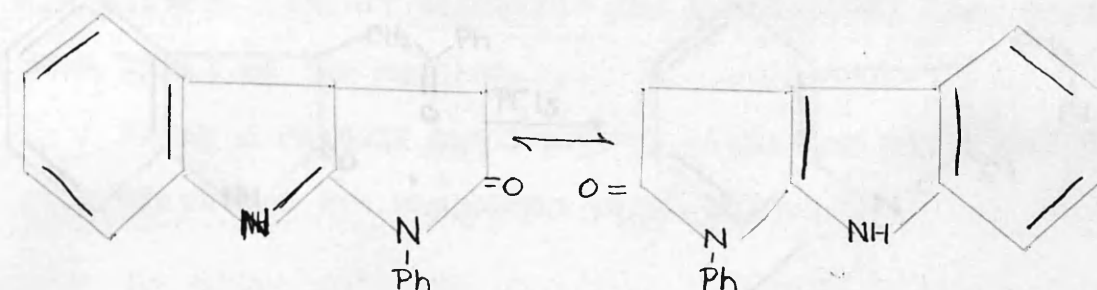


Following this idea, the mechanism suggested for the reaction in this case is shown below.

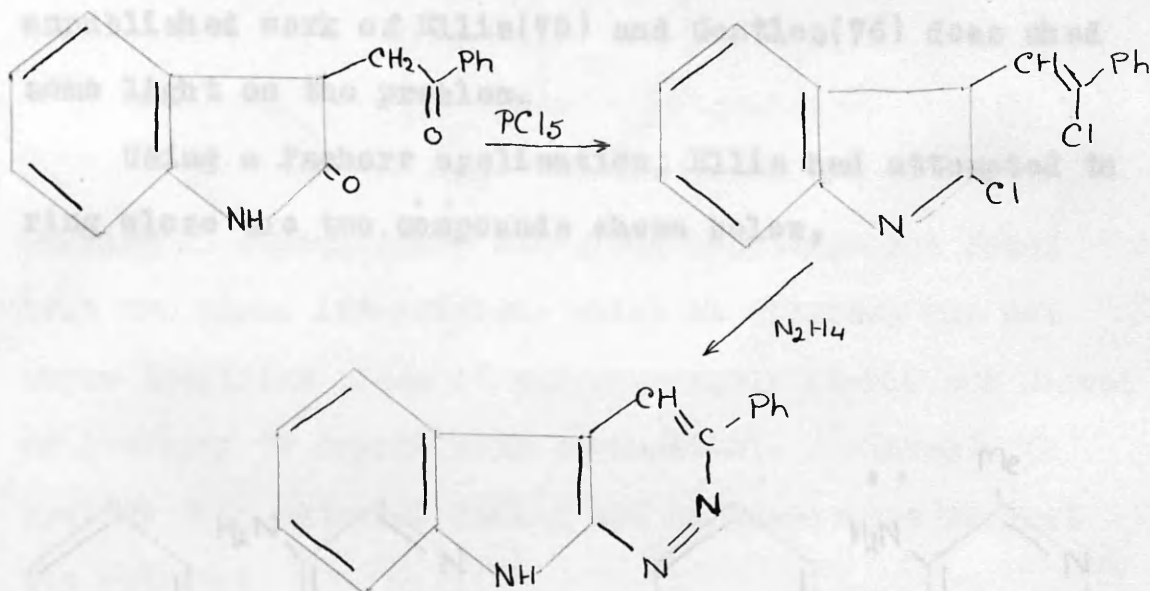


The infra-red spectrum of this compound is recorded and it does give some support to the formula suggested. The peaks are all rather small but a definite peak is to be noted at a wave-number of 1675 which is consistent with a tertiary amide group with a phenyl group on the nitrogen atom.

It also seems that there is little indication of a peak due to an NH group and for this reason a resonance structure is likely.



An attempt was also made to chlorinate 3-phenacyl-oxindole so that the resulting chloro compound might yield the required carbazole by treatment with hydrazine hydrate.



This attempted chlorination was also unsuccessful and the attempt to synthesise the carbazole by this route had also to be abandoned.

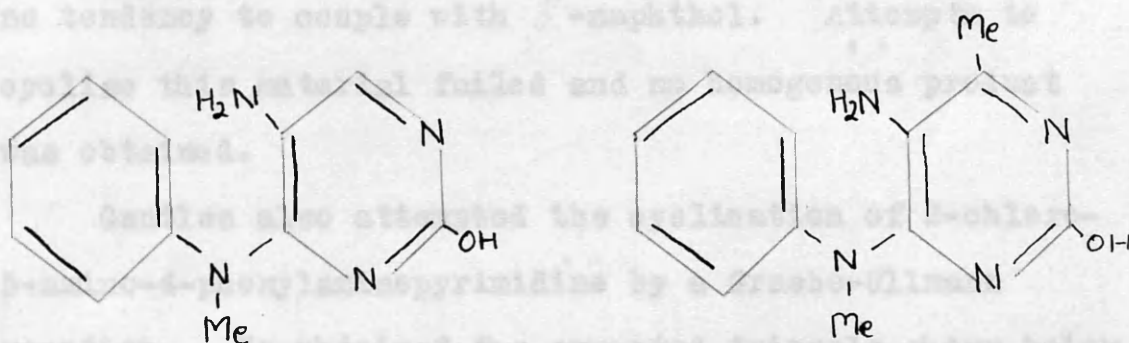
Thus although unsuccessful in its original concept this work on isatin yielded several new compounds and also lends further support to the mechanism suggested by Lindwall and MacLennan for the formation of cinchophen.

Thus the attempts to prepare 1:2-diazacarbazoles have in general failed at a vital stage. Some measure of success was achieved using polyphosphoric acid as reagent in the Borsche type synthesis but this yielded only a small amount of the tetrahydro compound and a considerable amount of work to improve the yield must be done before this method can be ready for publication.

Attempts were now made to synthesise the analogous 1:3-diazacarbazole system.

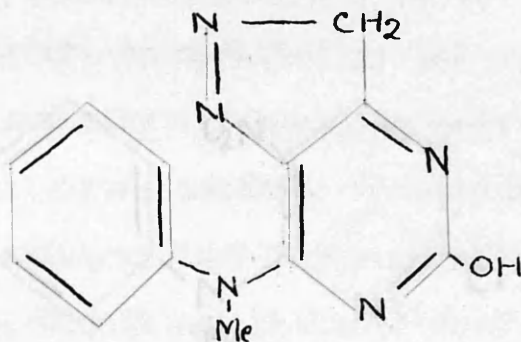
Little work has been done in this field but the unpublished work of Ellis(75) and Gentles(76) does shed some light on the problem.

Using a Pschorr cyclisation, Ellis had attempted to ring close the two compounds shown below,



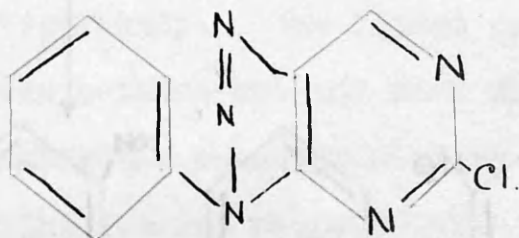
but he did not obtain the desired products. In the first case a product of inconsistent melting point was obtained and Ellis was never able to obtain this in a pure form; in the second instance cyclisation occurred with the adjacent methyl group to yield the compound shown below.





Gentles re-investigated the first substance but found that the diazo intermediate which he obtained was not above suspicion since it was remarkably stable and showed no tendency to couple with  $\beta$ -naphthol. Attempts to cyclise this material failed and no homogenous product was obtained.

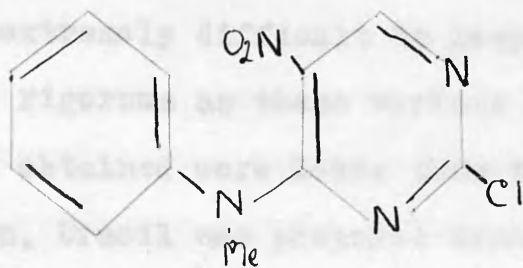
Gentles also attempted the cyclisation of 2-chloro-5-amino-4-phenylaminopyrimidine by a Graebe-Ullmann reaction. He obtained the expected triazole shown below,



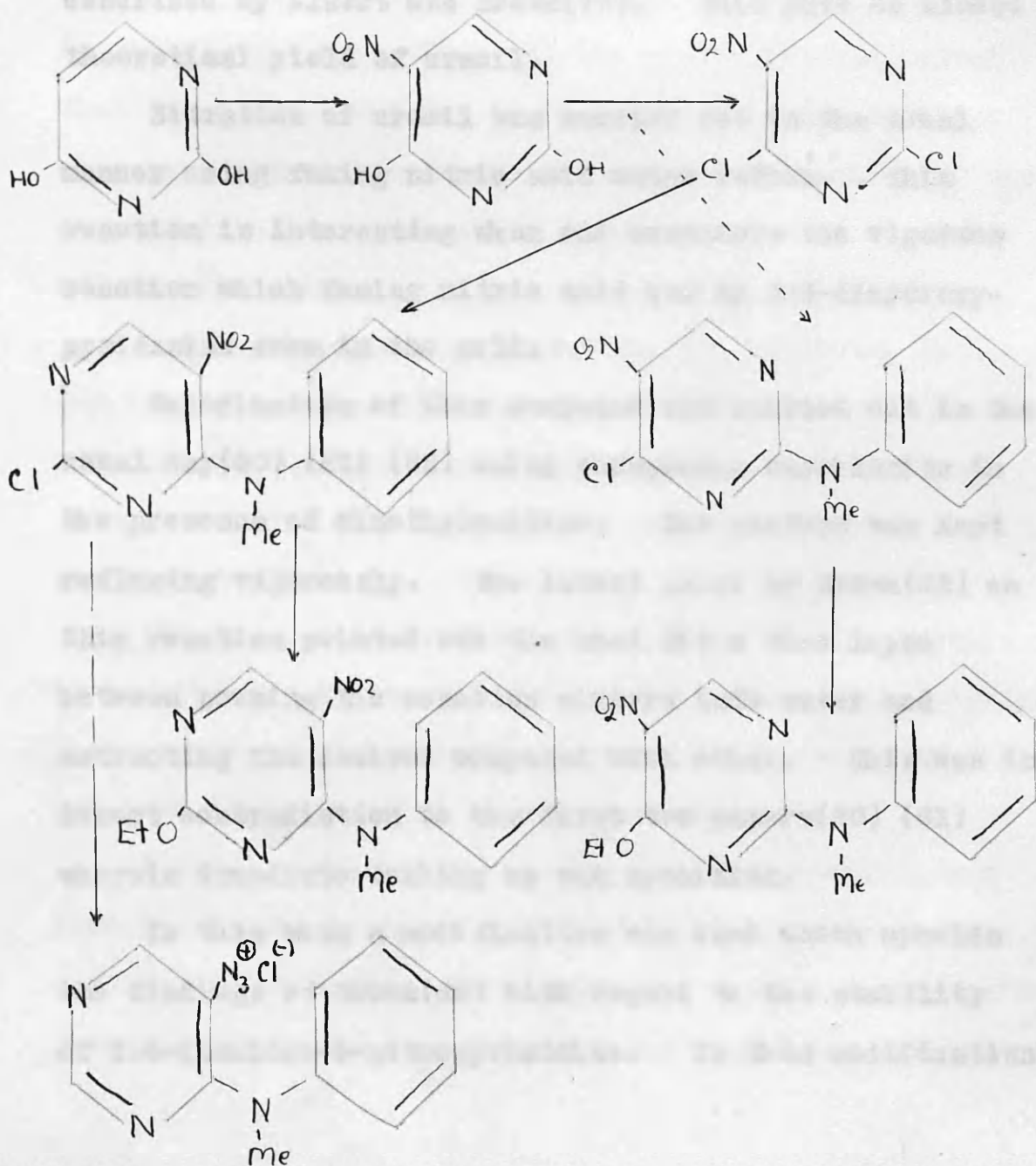
but on attempting its pyrolytic cleavage he obtained only a trace of material which seemed to be 2-chloro-1:3-diazacarbazole.

An attempt was now made to cyclise the analogous

compound shown below.



The reaction sequence followed is shown below.



Uracil was first prepared by the method of Davidson and Baudisch(77) as modified by Chi and Chen(78). It was found extremely difficult to keep the temperature control as rigorous as these workers had suggested and the yields obtained were lower than those claimed. For this reason, Uracil was prepared from the commercially available thio-uracil by the use of chloroacetic acid as described by Albert and Brown(79). This gave an almost theoretical yield of uracil.

Nitration of uracil was carried out in the usual manner using fuming nitric acid under reflux. This reaction is interesting when one considers the vigorous reaction which fuming nitric acid had on 3:6-dihydroxypyridazine even in the cold.

Chlorination of this compound was carried out in the usual way(80) (81) (82) using phosphorus oxychloride in the presence of dimethylaniline. The mixture was kept refluxing vigorously. The latest paper by Brown(82) on this reaction pointed out the need for a time lapse between pouring the reaction mixture into water and extracting the desired compound with ether. This was in direct contradiction to the first two papers(80) (81) wherein immediate working up was specified.

In this work a modification was used which upholds the findings of Brown(83) with regard to the stability of 2:4-dichloro-5-nitropyrimidine. In this modification



it was found necessary to wash the extract obtained with a little sodium bicarbonate solution to remove the last traces of acid.

At this stage it was noted that if a larger quantity of dimethylaniline was employed in the reaction and the time of reaction was shortened then another product was formed - 4-chloro-2-methylphenylamino- 5 -nitropyrimidine. This type of reaction has been noted before(84) (85) and in this latter paper King and his co-workers had proved that the product was due to replacement of the 2-chloro atom by a methylphenylamino fragment. This compound was converted to its ethyl ether by treatment with ethanol and caustic soda.

2:4-dichloro-5-nitropyrimidine was converted to 2-chloro-4-methylphenylamino-5-nitropyrimidine by treatment with n-methylaniline in ethanol at 0°C. Care must be taken here as double replacement occurs at higher temperatures(75).

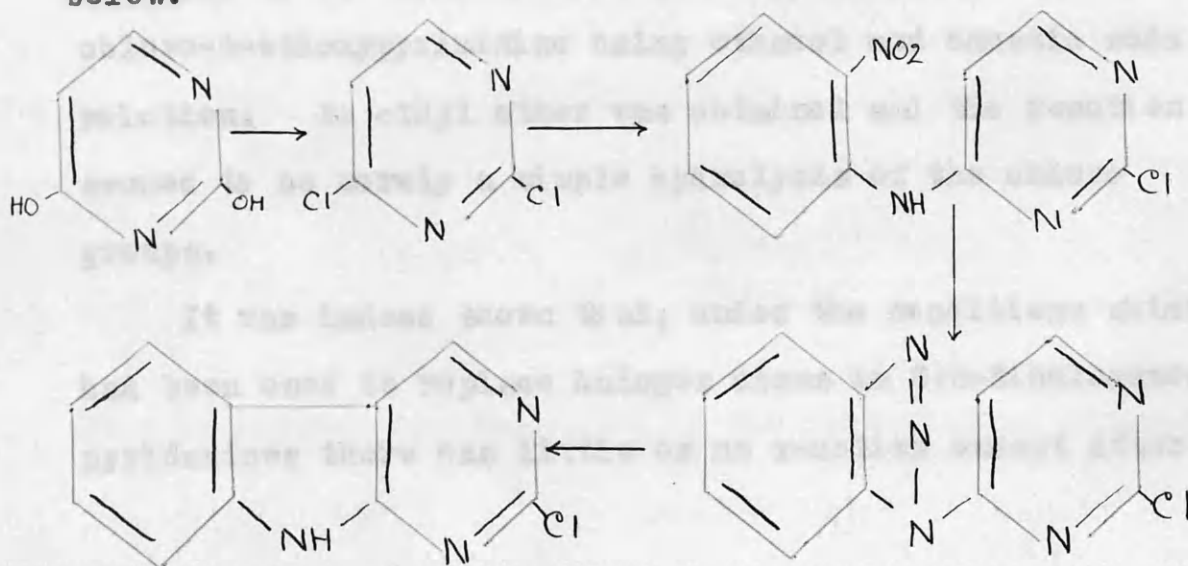
This compound was then converted to its ethyl ether by treatment with ethanol and caustic soda. This yielded 2-ethoxy-4-methylphenylamino-5-nitropyrimidine. In this way both isomeric ethyl ethers were prepared.

2-Chloro-4-methylphenylamino-5-nitropyrimidine was then reduced by means of a palladium/strontium carbonate catalyst in ethanol. This reduction removed the chlorine from the 2-position and the amine hydrochloride was isolated.

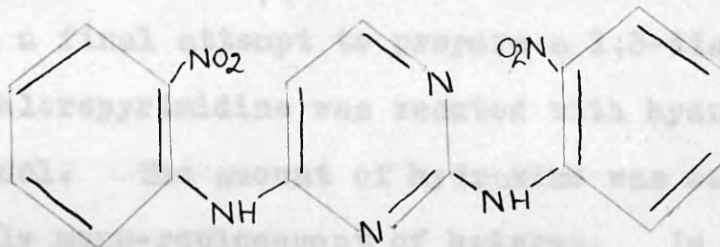
Attempts were then made to cyclise this material by a Pschorr type of cyclisation. A variety of methods were employed, but, in all cases it was found that the formation of a diazo intermediate was impossible as there was a copious evolution of nitrogen even at  $0^{\circ}\text{C}$ . This type of difficulty has been noted previously(81) by Whittaker in the case of 5-amino-pyrimidine. The fact that this decomposition occurred and that Gentles(76) had been able to isolate a stable diazonium compound gives support to Whittakers contention that "the ability to form diazo-compounds may well be confined to those 5-aminopyrimidines with at least one hydroxyl substituent".

Thus the attempted cyclisation of our compound was unsuccessful and a new approach to 1:3-diazacarbazole had to be found.

It was thought that a Graebe-Ullmann type of synthesis similar to that used by Gentles(76) might offer a solution to the problem. The proposed reaction sequence is shown below.



The initial stage was carried out using our modified chlorination procedure and gave a good yield of 2:4-dichloropyrimidine. On treating this compound with o-nitroaniline it was found that only a double condensation product was obtained.



At low temperatures there was no reaction and at more elevated temperatures both chlorine atoms were replaced.

This is somewhat similar to the action of aniline on 3:6-dichloropyridazine. In that instance however, it was found possible to obtain 3-anilino-6-chloropyridazine by reacting aniline with 3-chloro-6-ethoxypyridazine.

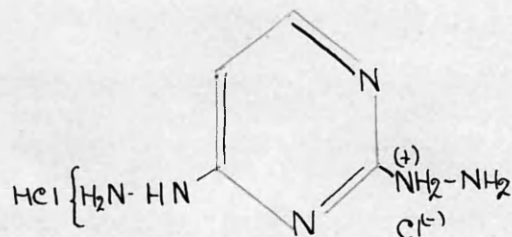
For this reason an attempt was made to prepare 2-chloro-4-ethoxypyrimidine using ethanol and caustic soda solution. No ethyl ether was obtained and the reaction seemed to be merely a simple hydrolysis of the chloro groups.

It was indeed shown that, under the conditions which had been used to replace halogen atoms in 3:6-dihalogenopyridazines there was little or no reaction except after

longer treatment in methanol and ethanol. Even after longer treatment n-propanol and caustic soda solution appeared to have no effect on 2:4-dichloropyrimidine. Thus it would appear that the halogen atoms in 2:4-dichloropyrimidine are less easily replaced than the halogen atoms of the pyridazine analogue.

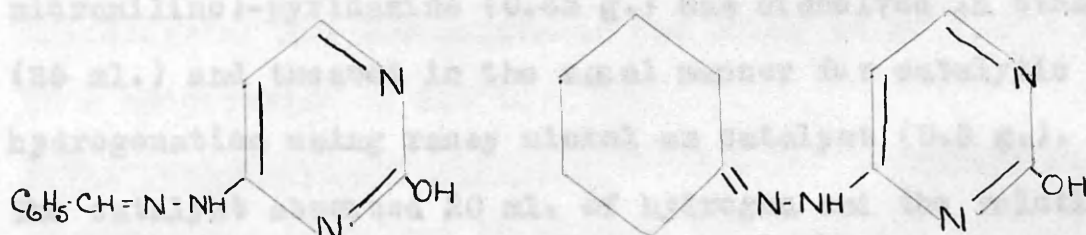
In a final attempt to prepare a 1:3-diazacarbazole 2:4-dichloropyrimidine was reacted with hydrazine hydrate in ethanol. The amount of hydrazine was calculated to give only mono-replacement of halogen. In all cases, double replacement occurred which seemed to give a dihydrazino-dihydrochloride. This double replacement had also been noted previously under more vigorous conditions by Boarland, McOmie and Timms(25). The exact nature of the product obtained was not too clear.

However, from later work of Timms(86) it seems more plausible that what has in fact occurred is firstly a simple replacement by hydrazine and secondly a quaternisation in the 2-position to give the compound shown.



This is further substantiated by the fact that an attempt

to react this compound with cyclohexanone and benzaldehyde has yielded the hydroxy compounds shown below.



In the time available no further work could be carried out on these compounds.

Thus the most promising method of obtaining a 1:3-diazacarbazole seems to be by a Borsche type synthesis on the cyclohexanone compound shown above, though even here there is the difficulty in the final stages of ring closing onto a very inactive ring system.

EXPERIMENTAL

3-Bromo-6-(o-aminoanilino)pyridazine.- 3-Bromo-6-(o-nitranilino)-pyridazine (0.45 g.) was dissolved in ethanol (25 ml.) and treated in the usual manner for catalytic hydrogenation using raney nickel as catalyst (0.5 g.).

The catalyst absorbed 20 ml. of hydrogen and the solution absorbed 113 ml. of hydrogen. The time of reduction was 50 minutes. The product isolated from the solution was an orange brown solid, which, on recrystallisation from methanol gave 3-Bromo-6-(o-aminoanilino)pyridazine as cream needles m.p. 153-4°C. (Found: C, 45.39; H, 3.26; N, 21.4.  $C_{10}H_9N_4Br$  requires C, 45.3; H, 3.42; N, 21.13%).

Picrate Derivative.- The above compound was dissolved in ethanol and a concentrated solution of picric acid in ethanol was added. On standing, yellow microneedles were deposited. These, after recrystallisation from ethanol, gave yellow needles, m.p. 149°C (d) (Found: N, 19.86.  $C_{16}H_{12}O_7N_7Br$  requires N, 19.84%).

1-(p-Bromopyridazino)-1:2:3-benzotriazole.- 3-Bromo-6-(o-aminoanilino)-pyridazine (0.5 g.) was dissolved in the minimum amount of glacial acetic acid and an equivalent amount of sodium nitrite was added. Immediately a solid was deposited, which, after recrystallisation from ethanol, yielded the above triazole as white needle crystals m.p. 193-194°C(S). (Found: C, 43.4; H, 2.33; N, 25.06:

$C_{10}H_6N_5Br$  requires C, 43.5: H, 2.19: N, 25.37%).

Attempts to convert this compound to the corresponding carbazole by heating and subsequent loss of nitrogen were unsuccessful and the substance was found to be stable up to a temperature of  $250^{\circ}C$ .

3-Chloro-6-hydrazinopyridazine.- 3:6-Dichloropyridazine (1.5 g.) was dissolved in ethanol (20 ml.) and hydrazine hydrate 100% (0.5 g.) was added. On evaporation of some of the alcohol, white solid was obtained, which, on recrystallisation from methyl acetate/petroleum ether (40-60) (2:1), yielded 3-Chloro-6-hydrazinopyridazine as white microcrystals m.p.  $139^{\circ}C$  (1.2 g. 85%) (Found: C, 33.06: H, 3.62: N, 38.93.  $C_4H_5N_4Cl$  requires C, 33.21: H, 3.49: N, 38.74%).

3-Hydrazino-6-chloropyridazine in ethanol on treatment with cyclohexanone yielded a hydrazone which was recrystallised from acetic acid to yield cream microcrystals, m.p.  $153-4^{\circ}C$ . (Found: C, 53.47: H, 5.71: N, 24.99.

$C_{10}H_{13}N_4Cl$  requires C, 53.45: H, 5.83: N, 24.94%).

3-( $\beta$ -acetylhydrazinol-6-hydroxypyridazine.- Cyclohexanone hydrazone (0.5 g.) was dissolved in glacial acetic (15 ml.) and concentrated hydrochloric acid (8 ml.) was added. The mixture was then refluxed for two hours. It was then poured into water, neutralised with caustic soda and extracted with ether. The extract, which had a marked blue fluorescence under ultra-violet light, yielded an



off white solid which sublimed to white needles at  $170^{\circ}\text{C}$ . The original product, crystallised from petroleum ether (60-80) and benzene, gave a m.p. of  $110-111^{\circ}\text{C}$ . (Found: C, 41.03; H, 4.98; N, 32.63.  $\text{C}_6\text{H}_8\text{O}_2\text{N}_4 \cdot \frac{1}{2}\text{H}_2\text{O}$  requires C, 40.8; H, 5.1; N, 31.6%).

3-Chloro-5:6:7:8-tetrahydro-1:2-diazacarbazole.- The cyclohexanone hydrazone (1.0 g.) was heated with polyphosphoric acid at  $180^{\circ}\text{C}$  till the mixture had become brown in colour. It was then poured into water, neutralised with caustic soda, and extracted with chloroform. The extract yielded a small amount of resinous material which was crystallised from petroleum ether (60-80) to yield 3-Chloro-5:6:7:8-tetrahydro-1:2-diazacarbazole as cream micro-crystals softening at  $128^{\circ}\text{C}$  m.p.  $145^{\circ}\text{C}$ . (Found: C, 52.93; H, 5.31.  $\text{C}_{10}\text{H}_{10}\text{N}_2\text{Cl} \cdot \text{H}_2\text{O}$  requires C, 53.21; H, 5.32%). The quantity obtained was only 4-5 mg.

Picrate Derivative.- The above compound was dissolved in ethanol and a saturated solution of picric acid in ethanol was added. On standing green-yellow micro-crystals were obtained which when recrystallised from ethanol gave m.p.  $217^{\circ}-218^{\circ}\text{C}$ . (Found: C, 43.84; H, 3.14; N, 19.36.  $\text{C}_{16}\text{H}_{13}\text{O}_7\text{N}_6\text{Cl}$  requires C, 44.00; H, 3.0; N, 19.24%).

It was found that heating with polyphosphoric acid at temperatures greater than  $180^{\circ}\text{C}$  gave only intractible



resins; whilst at temperatures below  $180^{\circ}\text{C}$  the starting material was returned unchanged.

Cyclohexanone hydrazone (1.0 g.) was heated with concentrated sulphuric acid (10 ml.) at  $120^{\circ}\text{C}$  for fifteen minutes. On pouring the reaction mixture into water and isolating the product it was found that the starting material was returned unchanged (0.9 g. 90%).

Cyclohexanone hydrazone (1.0 g.) was heated with zinc chloride (5.0 g.) at a temperature of  $190^{\circ}\text{C}$  for a time of twenty minutes. The mixture was poured into water and on isolating the product it was again found that the starting material was returned unchanged.

3-Chloro-6(*o*-chloranilino)pyridazine.- 3:6-Dichloro-pyridazine (1.5 g.) was mixed with *o*-chloroaniline (1.27 g.) and powdered potassium carbonate (1.38 g.) and the mixture heated on an oil-bath at  $137^{\circ}\text{C}$  for 30 minutes. The resulting mass was dark brown and was recrystallised from methanol to yield 3-Chloro-6-(*o*-chloranilino)pyridazine as cream needles m.p.  $122^{\circ}\text{C}$  (2.0 g. 83%). (Found: C, 49.71: H, 2.97: N, 17.17.  $\text{C}_{10}\text{H}_7\text{N}_3\text{Cl}_2$  requires C, 50.02: H, 2.94: N, 17.5%).

This compound was also identified by its picrate which was prepared in ethanolic solution. Crystallisation from ethanol gave yellow platelets m.p.  $173-4^{\circ}\text{C}$ . (Found: N, 17.85.  $\text{C}_{16}\text{H}_{10}\text{O}_7\text{N}_6\text{Cl}_2$  requires N, 17.91%).

3-Chloro-1:2-diazacarbazole.- 3-Chloro-6-(o-chloranilino)-pyridazine (1.0 g.) was heated with zinc chloride (5.0 g.) at 220° for twenty minutes. On pouring into water and isolating the product it was found that the starting material was returned unchanged (0.8 g. 80%). A similar result was obtained when the reagent employed was aluminium chloride at a temperature of 240°C for 30 minutes.

3-Formylindole.- Indole (12.5 g.) was reacted with sodium (3.33 g.) in presence of pyridine (12.5 g.) and ethyl oxalate (17.5 g.) and dry ethanol (62.5 ml.) as described by Hem's. This yielded the glyoxaline derivative of indole. This was then hydrolysed and then converted to the corresponding anil derivative. The anil was decomposed by boiling for one hour in anisole to yield 3-Formylindole (0.56 g. 36%) as cream micro-crystals m.p. 198°C.

3-Formylindole.- Dimethylformamide (87.0 g.) was cooled to -5°C and phosphorus oxychloride (30.68 g.) added with stirring so that the temperature does not exceed 10°C. Indole (11.7 g.) was then added keeping the temperature at 23-27°C and the mixture stirred for 30 minutes. Calcium carbonate (40 g.) was then added and temperature raised to 30-35°C whereafter it slowly rises to about 60°C in 30 minutes without further heating. Mixture was then cooled to 10°C and sodium acetate solution (200 ml. 30%) was added and the mixture diluted to 1 litre caustic soda (47.2 g.) was then added and the solution boiled for 3 hours.

after which it was steam distilled to remove unreacted indole, diluted to 3.5 litres and allowed to cool. On standing 3-Formylindole was precipitated as cream micro-crystals m.p.  $198^{\circ}\text{C}$  (10.4 g. 72%). This was the method of Tyson and Shaw.

3-Formylindole (modified procedure).- Dimethylformamide (35 g.) was cooled in an ice bath and phosphorus oxychloride (18 g.) was slowly added with stirring. Indole (11.7 g.) in dimethylformamide (10 g.) was then slowly added. The reaction is merely kept controlled by the ice-bath, the internal temperature being allowed to rise to about  $35^{\circ}\text{C}$ . The mixture was then stirred for 30 minutes at this temperature and then poured onto crushed ice (200 g.). The resulting solution was made just alkaline with caustic soda (5 N) and the mixture boiled for 20 minutes. On cooling 3-Formylindole was deposited, m.p.  $198^{\circ}\text{C}$  (11.2 g. 85%).

1-Methylindole.- Indole (11.7 g.) in ether (20 ml.) was added to sodium (2.5 g.) in liquid ammonia (200 ml.) in the presence of ferric nitrate (0.1 g.), and methyl iodide (16 g.) added according to the method of Potts and Saxton. Product was 1-Methylindole b.p.  $133^{\circ}$  at 26 mm. pressure ( $n_{\text{D}}^{18.5} = 1.6082$ ). The yield was 11.6 g. (80%).

1-Methylindole.- Indole (11.7 g.) was dissolved in acetone (50 ml.) and potassium hydroxide powder (6.0 g.) added. Methyl iodide (15 g.) was then added and the reaction

mixture refluxed gently for thirty minutes. Acetone was removed by distillation and the residue was then distilled under reduced pressure, the fraction boiling at 133-135°C at 26 mm. pressure being collected. This gave 1-Methyl-indole as a colourless oil (7.8 g. 60%) ( $n_d^{22} = 1.6148$ ).

1-Methyl-3-formylindole.- 1-Methylindole (14.5 g.) in dimethylformamide (10 g.) was slowly added to a mixture of dimethylformamide (35 g.) and phosphorus oxychloride (18 g.) cooled by an ice bath. The temperature was allowed to rise to 35°C and was maintained at this point for 30 minutes. The reaction mixture was then poured onto crushed ice (200 g.), made just alkaline with caustic soda (5 N) and the solution then boiled for 30 minutes. On cooling 1-Methyl-3-formylindole was precipitated as cream micro-crystals m.p. 65°C (11.0 g. 68%).

1-Methyl-3-formylindole.- 3-Formylindole (2.9 g.) was dissolved in a mixture of caustic soda (5 N 50 ml.) and methyl sulphate (3.5 g.). On standing an oil is deposited which slowly goes to a reddish-brown solid. On crystallisation from methanol this yielded 1-Methyl-3-formylindole as cream micro-crystals m.p. 65°C (2.0 g. 50%). This is the method Wieland Konz and Mittasch.

β-Indolylacrylic acid.- 3-Formylindole (1.45 g.) was dissolved in pyridine (10 ml.) and a trace of piperidine added. To this solution was added malonic acid (1.04 g.)

and the reaction mixture heated on a water bath for three hours. The reaction mixture darkened and carbon dioxide was evolved. On pouring into dilute hydrochloric acid and allowing to stand the only product was an intractible red resin.

Modified procedure.- 3-Formylindole (1.45 g.) was dissolved in pyridine (10 ml.) and a trace of piperidine added. To this solution was added malonic acid (1.04 g.) and the reaction mixture warmed to 40°C for ten minutes and then allowed to stand at room temperature for 3 hours. The mixture was then rendered just acid (pH=5) by dilute hydrochloric and a yellow crystalline compound was obtained. This on crystallisation from methyl cyanide yielded  $\beta$ -Indolylacrylic acid as red needles m.p. 194°C (1.14 g. 60%) (Found: C, 70.37; H, 4.91; N, 7.7.  $C_{11}H_9O_2N$  requires C, 70.57; H, 4.85; N, 7.48%). If crystallised from non-polar solvents such as benzene/petroleum ether the product is in the form of white micro-crystals m.p. 158°C (d) which seem to be partially decarboxylated material. Crystallisation of this material from methyl cyanide also yielded a pure specimen of  $\beta$ -Indolylacrylic acid m.p. 194°C.

1:1-Dicarboxy-2:3'-(1-methylindolyl)ethylene.- 1-Methyl-3-formylindole (1.59 g.) was dissolved in pyridine (10 ml.) and a trace of piperidine was added. Malonic acid (1.04 g.) was then added and the reaction mixture warmed to 40°C for ten minutes and then allowed to stand for three hours

at room temperature. The reaction mixture was poured into water (25 ml.) and rendered acid (pH=5) by means of dilute hydrochloric acid. This yielded a yellow crystalline precipitate. On crystallisation from methyl cyanide this yielded 1:1-Dicarboxy-2:3'-(1-methylindolyl)ethylene (1.72 g. 74%) as greenish-yellow needles m.p. 195°C (Found: C, 63.60; H, 4.61; N, 5.97.  $C_{13}H_{11}O_4N$  requires C, 63.67; H, 4.52; N, 5.97%).

Ethylhydrazodicarboxylate.- Hydrazine hydrate (59 g. 85%) in ethanol (500 ml. 95%) was reacted slowly with ethyl chloroformate (217 g.) at a temperature of 15-20°C, as described by Rabjohn in Organic Syntheses. This yields Ethylhydrazodicarboxylate (150 g. 85%) as white needles m.p. 133°C.

Ethylazodicarboxylate.- Ethylhydrazodicarboxylate (100 g.) in benzene (500 ml.) and water (500 ml.) was oxidised by chlorine gas (55 g.) at a temperature of 15°C as described by Rabjohn. This yielded Ethylazodicarboxylate (80 g. 81%) as a red oil b.p. 107-111°C at 15 mm. press.  $n_D^{19} = 1.4274$ . This product was further characterised by the formation of an adduct with diphenylbutadiene.

1:2-Dicarbethoxy-3:6-diphenyl-1:2:3:6-tetrahydropyridazine.- Ethylazodicarboxylate (1.74 g.) was mixed with diphenylbutadiene (2.06 g.) and the mixture heated for one hour at 100°C. Crystallisation from methyl cyanide gave 1:2-Dicarbethoxy-3:6-diphenyl-1:2:3:6-tetrahydropyridazine

(3.04 g. 80%) as white needles m.p.  $134^{\circ}\text{C}$  (Found: C, 69.41: H, 6.45: N, 7.5.  $\text{C}_{22}\text{H}_{24}\text{O}_4\text{N}_2$  requires C, 69.46: H, 6.36: N, 7.37%).

1:2-Dicarbethoxy-1:2:3:10-tetrahydro-1:2-diazacarbazole.-

$\beta$ -Indolyacrylic acid (0.93 g.) was mixed with ethylazodicarboxylate (0.92 g.) in benzene (20 ml.) and the mixture refluxed for 3 hours. No visible change occurred.

Benzene was removed and on vacuum distillation ethylazodicarboxylate (0.9 g.) was recovered unchanged.

$\beta$ -Indolyacrylic acid (0.93 g.) was then mixed with ethylazodicarboxylate (0.92 g.) as above and a trace of hydrochloric acid added (2 drops). In this case the weight of ethylazodicarboxylate recovered was (0.8 g.).

$\beta$ -Indolyacrylic acid (0.93 g.) was mixed with ethylazodicarboxylate (0.92 g.) and the mixture heated to  $130^{\circ}\text{C}$  for 3 hours. The mixture darkened and became viscid. The only product obtained on cooling was an intractible brown resin.

1:2-Dicarbethoxy-1:2:3:10-tetrahydro-9-methyl-1:2-

diazacarbazole.- Using 1:1-Dicarboxy-2-(1-methylindolyl)-ethylene (1.16 g.) and ethylazodicarboxylate (0.92 g.)

The three experiments detailed above were repeated exactly.

The results obtained were wholly analogous.

3-Hydroxy-3-phenacyloxindole.- Isatin (5.0 g.) was mixed with acetophenone (4.0 g.) in ethanol (100 ml.) and diethylamine (10 drops) was added. The mixture was

allowed to stand overnight and yielded yellow needles which, crystallised from ethanol, gave 3-Hydroxy-3-phenacyloxindole m.p. 170-172°C (6.2 g. 63%) as described by Lindwall and Maclellan.

3-Hydrazino-oxindole.- 3-Hydroxy-3-phenacyloxindole (2.67 g.) was dissolved in ethanol (50 ml.) and hydrazine hydrate (100% 0.51 g.) was then added. The reaction mixture was heated for ten minutes. The mixture was poured into water and the yellow product was crystallised from a mixture of methanol and ethanol (1:1) to give 3-Hydrazino-oxindole as yellow plates m.p. 220° (d). (1.4 g. 87.5%) (Found: C, 59.47: H, 4.71.  $C_8H_7ON_3$  requires C, 59.61: H, 4.38%). This product was further characterised by forming its benzaldehyde derivative. 3-Hydrazino-oxindole (0.8 g.) and benzaldehyde (0.53 g.) were refluxed in ethanol (20 ml.) for fifteen minutes. An orange product separated on cooling. Crystallisation from ethanol gave the benzaldehyde derivative as orange prisms m.p. 198°C (1.1 g. 88%) (Found: C, 72.32: H, 4.42: N, 16.66.  $C_{15}H_{11}ON_3$  requires C, 72.30: H, 4.45: N, 16.84%).

3-Hydroxy-3-phenacyl-oxindole oxime.- 3-Hydroxy-3-phenacyl-oxindole (0.89 g.) was treated with hydroxylamine hydrochloride (0.23 g.) in the usual manner using a sodium acetate buffer. After fifteen minutes refluxing a cream product separated. On crystallisation from ethanol, this product gave 3-Hydroxy-3-phenacyl-oxindole oxime as



white micro-crystals m.p.  $198^{\circ}\text{C}$  (0.8 g. 81%) (Found:

N, 10.4.  $\text{C}_{16}\text{H}_{14}\text{O}_3\text{N}_2$  requires N, 9.94%).

3-Phenacylidene-oxindole.- 3-Hydroxy-3-phenacyloxindole (8.9 g.) was dissolved in ethanol (30 ml.) and concentrated hydrochloric acid (50 ml.) was added. The reaction mixture was heated at  $100^{\circ}\text{C}$  for one hour. The orange red product was crystallised from ethanol to give 3-Phenacylidene-oxindole as orange-red needles m.p.  $194^{\circ}\text{C}$  (7.6 g. 92%) as described by Lindwall and MacLennan. The product was also characterised by formation of its oxime by refluxing equimolecular amounts of neutralised hydroxylamine hydrochloride and 3-phenacylidene-oxindole in ethanol for fifteen minutes. This yielded 3-Phenacylidene-oxindole oxime orange-red plates m.p.  $253^{\circ}\text{C}$  (Found: N, 10.8.  $\text{C}_{16}\text{H}_{12}\text{O}_2\text{N}_2$  requires N, 10.6%).

3-Phenacylidene-oxindole hydrazone.- 3-Phenacylidene-oxindole (2.49 g) was dissolved in ethanol (50 ml.) and hydrazine hydrate (100% 0.5 g.) added. The mixture was refluxed for fifteen minutes and then cooled. A white crystalline product resulted. This product was crystallised from methanol to yield white prisms S.  $128^{\circ}\text{C}$  m.p.  $202^{\circ}\text{C}$ . This product was 3-Phenacylidene-oxindole hydrazone with one molecule of water of crystallisation (1.96 g. 70%) (Found: C, 68.65: H, 5.49: N, 15.04.  $\text{C}_{16}\text{H}_{13}\text{ON}_3\cdot\text{H}_2\text{O}$  requires C, 68.31: H, 5.4: N, 14.94%). This product was dried in

vacuum at 130°C for six hours to yield the unhydrated compound m.p. 202°C (Found: C, 73.21: H, 5.1: N, 16.01  $C_{16}H_{13}ON_3$  requires C, 72.99: H, 4.98: N, 15.96%).

Reference to the infra-red spectra of this and certain related compounds indicate that the isomeric pyrazolene structure is more likely.

3-Phenacyloxindole.- 3-Phenacylidene-oxindole (5 g.) was made into a slurry in ethanol (95% 75 ml.). To this was added sodium hyposulphite (5 g.) in water (25 ml.) and the reaction mixture warmed on a steam bath for twenty minutes as described by Lindwall & Maclellan. This yielded 3-Phenacyl-oxindole as white prisms m.p. 177°C (4.5 g. 89%).

3-Phenacyl-oxindole hydrazone.- 3-Phenacyl-oxindole (2.51 g.) was partly dissolved in ethanol (50 ml.) and hydrazine hydrate (100% 0.5 g.) was added. The mixture was refluxed for 30 minutes. On cooling a white crystalline product was formed. After recrystallisation from ethanol this gave white prismatic crystals of 3-Phenacyl-oxindole hydrazone m.p. 178°C (2.39 g. 91%). The m.m.p. with 3-phenacyl-oxindole was 157°C. (Found: C, 72.14: H, 5.85: N, 15.7.  $C_{16}H_{15}ON_3$  requires C, 72.4: H, 5.70: N, 15.87%).

3-Phenyl-4:11-dihydro-1:2-diazacarbazole.- 3-Phenacyl-oxindole hydrazone (1.3 g.) was refluxed in phosphorus trichloride (5 ml.) for 3 hours. There was no marked change in the appearance of the reaction mixture. The

mixture was cooled and poured onto ice. On crystallisation the product was shown, by m.p.  $175^{\circ}\text{C}$  and m.m.p.  $176^{\circ}\text{C}$  to be 3-Phenacyl-oxindole (1.0 g. 75%). (Found: C, 76.28; H, 4.9.  $\text{C}_{16}\text{H}_{13}\text{O}_2\text{N}$  requires C, 76.51; H, 5.18%). Treatment of the same weight of 3-Phenacyl-oxindole hydrazone with phosphorus oxychloride gave no cyclised product; only a dark intractible resin was obtained.

1-Phenyl-indolo(2':3':2:3)-5-hydroxypyrrole.- 3-Phenacyl-oxindole hydrazone (1.3 g.) was treated with polyphosphoric acid in the usual manner at a temperature of  $100^{\circ}\text{C}$  for 3 hours. On pouring into water a cream solid was obtained which was crystallised from aqueous ethanol to yield 1-Phenyl-indolo(2':3':2:3)-5-hydroxypyrrole as cream micro-crystals S.  $140^{\circ}\text{C}$  m.p.  $165^{\circ}\text{C}$  (Found: C, 77.94; H, 5.06; N, 11.40.  $\text{C}_{16}\text{H}_{12}\text{ON}_2$  requires C, 77.50; H, 4.75; N, 11.3%).

Uracil.- (a) This compound was prepared by the method of Davidson and Baudisch(77), as modified by Chi and Chen(78).

Urea (100 g.) was added slowly, with stirring to oleum (15%) (770 g.) which was cooled to  $-5^{\circ}\text{C}$ . The temperature must be held below  $0^{\circ}\text{C}$  or lower yields result. Malic acid (100 g.) was then added and temperature allowed to rise freely. The mixture was then heated ( $80-90^{\circ}\text{C}$ ) for one hour. Carbon monoxide and dioxide were evolved. After cooling, the contents were poured onto crushed ice (1200 g.). Crude uracil precipitated. This was

recrystallised from water to give white micro-crystals m.p.  $335^{\circ}\text{C}$  of weight, 30 g. (36% of theoretical).

(b) Also prepared by the method of Brown(79) wherein thiouracil (7.2 g.), chloroacetic acid (6.3 g.) and water (135 g.) were refluxed together for  $2\frac{1}{2}$  hours. This gave a clear solution, to which was added 10 N hydrochloric acid (20 ml.). On cooling uracil separated out. Recrystallised from water gave needles m.p.  $335^{\circ}\text{C}$  of weight 5.6 g. (88% of theoretical).

5-Nitrouracil.-- Uracil was nitrated by the method described by Ellis(75). Uracil (40 g.) was dissolved in fuming nitric acid (S.G. = 1.5: 120 ml.) and the mixture refluxed for one hour. This yielded 5-Nitrouracil of weight 52.2 g. (93% of theoretical).

2:4-Dichloro-5-nitropyrimidine.-- 5-Nitrouracil was chlorinated in the usual way using phosphorus oxychloride and dimethylaniline under reflux(80) (81) (82). This gave 2:4-Dichloro-5-nitropyrimidine as a yellow solid m.p.  $29^{\circ}\text{C}$  (40% of theoretical).

This was later modified. The reaction mixture was poured into water and the aqueous solution was allowed to stand for 30 minutes. The solution was then extracted with ether. The extract was washed with water dilute sodium bicarbonate and finally water. Evaporation of this extract appeared to give a purer product than when it was not treated with bicarbonate. The yield was exactly as

quoted in the previous papers.

4-Ethoxy-2-methylphenylamino-5-nitropyrimidine.- 5-nitro-uracil (1.6 g.) was suspended in phosphorus oxychloride (4.6 ml.) and dimethylaniline (1.9 ml.) and the whole refluxed for one hour. The black solution was cooled and poured onto ice (100 g.) and the mixture extracted with ether. The extract was washed with dilute hydrochloric, water, dilute sodium carbonate, water and dried over sodium sulphate. This gave a yellow solid which was recrystallised from ethanol and then from petroleum (60-80°C). This gave yellow needles m.p. 116-118°C (Found: C, 57.0; H, 5.2; N, 20.4.  $C_{13}H_{14}O_3N_4$  requires C, 56.9; H, 5.1; N, 20.4%).

2-Chloro-4-methylanilino-5-nitropyrimidine.- Methylaniline (3.8 ml.) in alcohol (11.2 ml.) was added with stirring to an ice-cold mixture of 2:4-dichloro-5-nitropyrimidine (3.37 g.) in alcohol (12 ml.) over a period of 3 hours. Product was crystallised from petroleum (100-120°C) to give 3.98 g. (86% theoretical) of yellow needles m.p. 128-129°C.

2-Ethoxy-4-methylanilino-5-nitropyrimidine.- 2-Chloro-4-methylanilino-5-nitropyrimidine (2.5 g.) was dissolved in ethanol (50 ml.) and sodium hydroxide (0.5 g.) added. There was no apparent reaction, but on filtering of the solid produced on cooling and testing the filtrate, free halogen was noted (silver nitrate test). The product

was recrystallised from petroleum (60-80°C) to give 2-Ethoxy-4-methylanilino-5-nitropyrimidine as yellow/green needles (2.4 g. 75% of theoretical) of m.p. 145°C (Found: C, 57.12; H, 5.15; N, 20.59.  $C_{13}H_{14}O_3N_4$  requires C, 56.93; H, 5.1; N, 20.4%).

5-Amino-4-methylanilinopyrimidine.- 2-Chloro-4-methylanilino-5-nitropyrimidine (1.06 g.) was dissolved in ethanol (25 ml.) and added to 5% palladised strontium carbonate (0.5 g.) saturated with hydrogen in ethanol (15 ml.). Hydrogen (350 ml.) was absorbed in 1½ hours. The solution was filtered and catalyst extracted with hot ethanol. The ethanol portions were combined and evaporated to 10 ml. when yellow/green crystals were deposited (0.42 g.).

These were recrystallised from ethanol/benzene mixture giving pale green, rectangular plates softening at 225° m.p. 250° (0.42 g. 44% of theoretical) (Found: C, 55.7; H, 5.3; N, 23.7.  $C_{11}H_{13}N_4Cl$  requires C, 55.8; H, 5.5; N, 23.7%).

Diazotisation.- The above hydrochloride (0.12 g.) was dissolved in hydrochloric acid (15% 1.2 ml.). The solution was cooled to -5°C and sodium nitrite (20% 0.3 ml.) added. Nitrogen evolution occurred at once and no diazonium salt could be isolated. The attempt was repeated using sulphuric acid (20% 2 ml.) in place of hydrochloric but the same gaseous evolution occurred.

2:4-Dichloropyrimidine.- Uracil (5.0 g.) was suspended in phosphorus oxychloride (25 ml.) and dimethylaniline (6.2 ml.). The mixture was refluxed under anhydrous conditions for 2 hours. The excess of phosphorus oxychloride was then distilled off and the residue poured into water. This solution was extracted with ether and the extract washed with dilute hydrochloric acid, water, sodium bicarbonate and water. It was then dried with magnesium sulphate and ether removed. This yielded 3.3 g. of yellow blades; recrystallised from petroleum (40-60) gave m.p.  $61^{\circ}\text{C}$  (3.2 g. 50% of theoretical).

2:4-Di(o-nitranilino)pyrimidine.- 2:4-Dichloropyrimidine (0.1 g.), o-nitraniline (0.08 g.), trace of copper bronze and potassium carbonate (0.05 g.) were heated together, by means of an oil bath, to  $130^{\circ}\text{C}$  when a brisk reaction occurred. The mixture was maintained at this temperature for 30 minutes when the melt had re-solidified. Recrystallisation from benzene yielded 2:4-Di(o-nitranilino)pyrimidine as yellow needles, m.p.  $218-219^{\circ}\text{C}$  (Found: C, 54.88: H, 3.44: N, 24.23.  $\text{C}_{16}\text{H}_{12}\text{O}_4\text{N}_6$  requires C, 54.54; H, 3.43: N, 23.86%).

2:4-Dihydrazinopyrimidine.- 2:4-Dichloropyrimidine (1.5 g.) was dissolved in warm ethanol (20 ml.) and hydrazine hydrate (100% 0.5 g.) carefully added. There was a vigorous reaction and a cream solid was produced. This was recrystallised from methanol to give the dihydrochloride of



2:4-Dihydrazinopyrimidine as cream/white needles, softening and decomposing above  $220^{\circ}\text{C}$  m.p.  $290^{\circ}\text{C}$  (Found: C, 22.53: H, 4.98: N, 39.18.  $\text{C}_4\text{H}_{10}\text{N}_6\text{Cl}_2$  requires C, 22.53: H, 4.73: N, 39.43%).

Benzaldehyde derivative.- The above compound (2.13 g.) was dissolved in ethanol (25 ml.) and benzaldehyde (1.06 g.) was added. The mixture was warmed and a white precipitate was formed. This was recrystallised from glacial acetic acid to yield the 2-Hydroxypyrimidylhydrazone of benzaldehyde as its mono-hydrate m.p.  $241^{\circ}\text{C}$  (2.0 g. 85%) (Found: N, 24.16.  $\text{C}_{11}\text{H}_{12}\text{O}_2\text{N}_4$  requires N, 24.15%).

Cyclohexanone derivative.- The compound (2.13 g.) was dissolved in ethanol (25 ml.) and cyclohexanone (0.98 g.) was added. The mixture was refluxed for one hour. On cooling and pouring into water the 2-Hydroxypyrimidylhydrazone of cyclohexanone was obtained. Recrystallisation from methanol gave cream prisms m.p.  $161^{\circ}\text{C}$  (2.0 g. 94%) (Found: N, 25.56.  $\text{C}_{10}\text{H}_{16}\text{O}_2\text{N}_4$  requires N, 25.02%).

2-Chloro-4-methoxypyrimidine.- 2:4-Dichloropyrimidine (1.5 g.) was dissolved in methanol (5 ml.) and added to a slight excess of a concentrated solution of potassium hydroxide in methanol. The mixture was allowed to stand for thirty minutes and was then poured into water. The aqueous solution was extracted with ether. This extract yielded unchanged 2:4-dichloropyrimidine (0.73 g. 49%) and nothing else. Halogen was shown present in solution by testing

with silver nitrate solution.

2-Chloro-4-ethoxypyrimidine.- 2:4-Dichloropyrimidine

(1.5 g.) was dissolved in ethanol and treated with a solution of potassium hydroxide in ethanol as described above. The only product was 2:4-dichloropyrimidine (0.67 g. 45%). Halogen was again shown present in solution by testing with silver nitrate solution.

2-Chloro-4-isopropoxypyrimidine.- 2:4-Dichloropyrimidine

(1.5 g.) was dissolved in iso-propanol (5 ml.) and added to a slight excess of potassium hydroxide dissolved in iso-propanol. The mixture was refluxed for thirty minutes. On allowing the reaction mixture to cool 2:4-dichloropyrimidine crystallised out (1.35 g. 90%).

## SUMMARY

Attempts to synthesise diazacarbazoles have shown that deactivation of the diazine ring system causes great difficulty in bringing about cyclisation in the usual synthetic methods.

3-Chloro-5:6:7:8-tetrahydro-1:2-diazacarbazole has however been prepared from the cyclohexanone derivative of 3-Chloro-6-hydrazino-pyridazine by the Borsche method.

A new synthesis of 1-methylindole has been established.

An interesting Beckmann reaction is suggested by the formation of 1-Phenyl-indolo(2':3':2:3)-5-hydroxypyrrole from 3-Phenacyl-oxindole hydrazone in the presence of polyphosphoric acid.

PART III

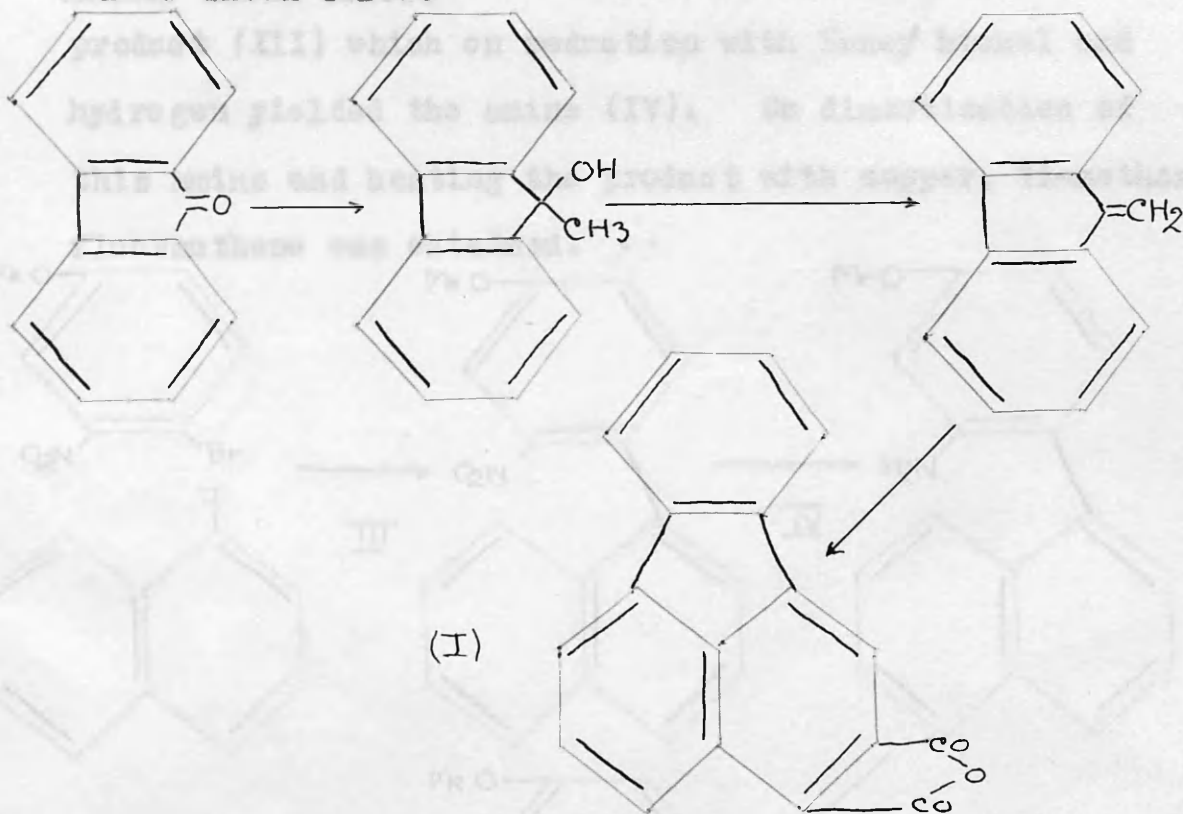
"SYNTHESIS OF 3-METHOXYFLUORANTHENE"

### INTRODUCTION

In most of its reactions, fluoranthene yields mono-derivatives which are nearly always mixed with disubstituted fluorenthenes.

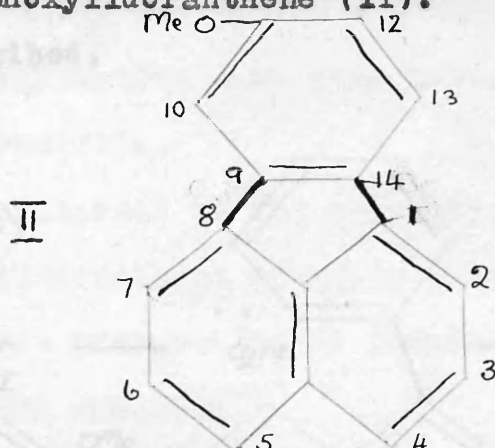
The separation of these products is usually a matter of considerable difficulty. As a result any synthesis which produces only one product is of considerable interest.

In 1949 Campbell & Wang(87) described the synthesis of fluoranthene-3:4-dicarboxylic acid anhydride (I) in the manner shown below.

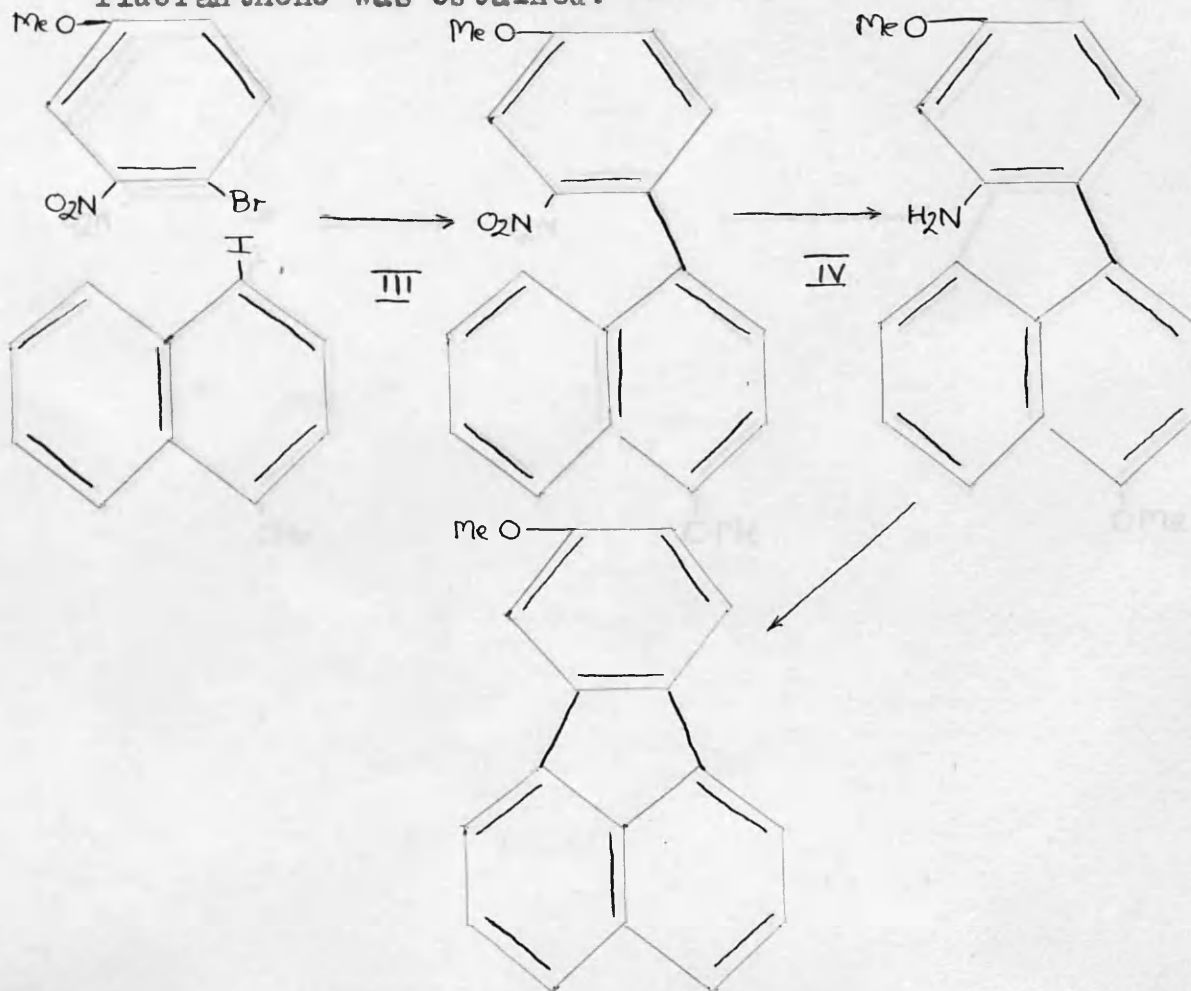


On subsequent hydrolysis and decarboxylation of this acid anhydride these workers claimed to have obtained fluorenone-3-carboxylic acid in low yield.

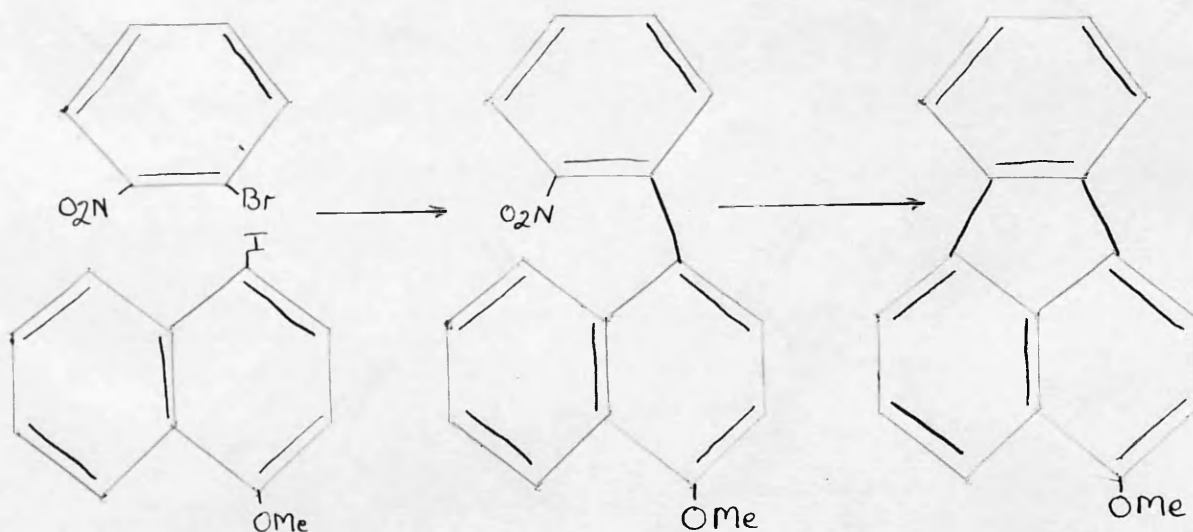
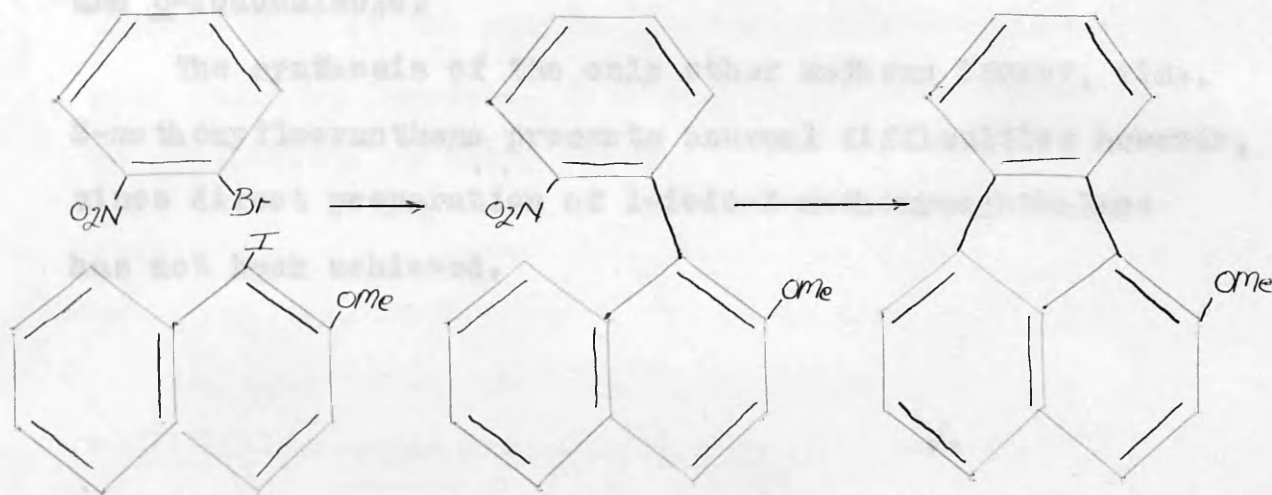
In 1950, Hawkins & Tucker(88) described a synthesis of 11-methoxyfluoranthene (II).



They condensed 1-iodonaphthalene by a crossed Ullmann reaction with 4-bromo-3-nitroanisole and obtained the product (III) which on reduction with Raney nickel and hydrogen yielded the amine (IV). On diazotisation of this amine and heating the product with copper, 11-methoxyfluoranthene was obtained.



In a later paper by Stubbs and Tucker(89) the syntheses of the 2-, and 4-methoxyfluoranthenes by analogous methods, are described.



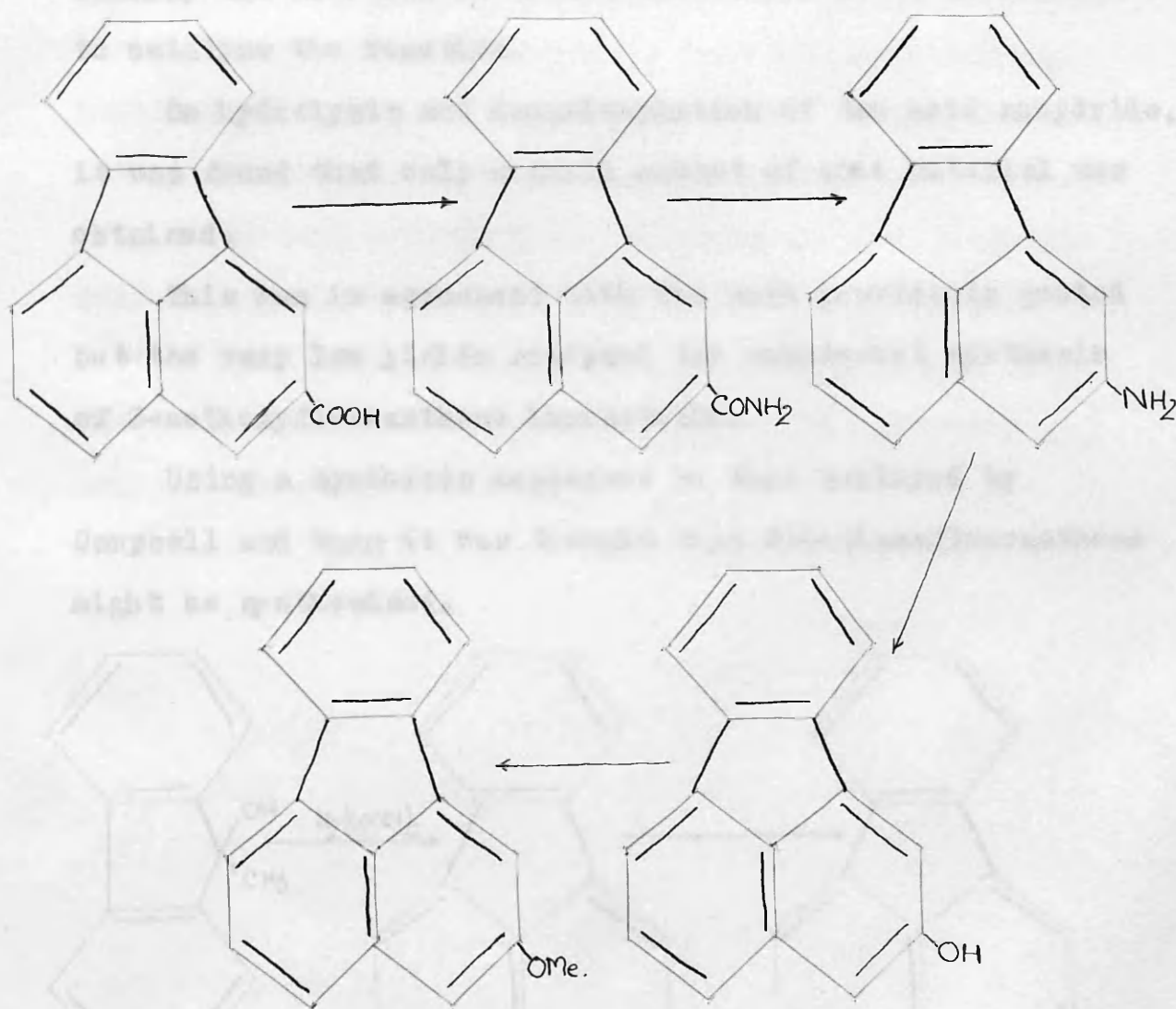
Having failed to prepare 10-methoxyfluoranthene by this general method, the method was modified by these workers. In the modification they used 1-bromo-8-nitronaphthalene and o-iodoanisole.

The synthesis of the only other methoxy isomer, viz., 3-methoxyfluoranthene presents unusual difficulties however, since direct preparation of 1-iodo-3-methoxynaphthalene has not been achieved.



### DISCUSSION

The synthesis of 3-methoxyfluoranthene was based initially on the work of Campbell and Wang(87). It was thought that if the yields of fluoranthene-3-carboxylic acid could be improved, then 3-methoxyfluoranthene might be synthesised as shown below.



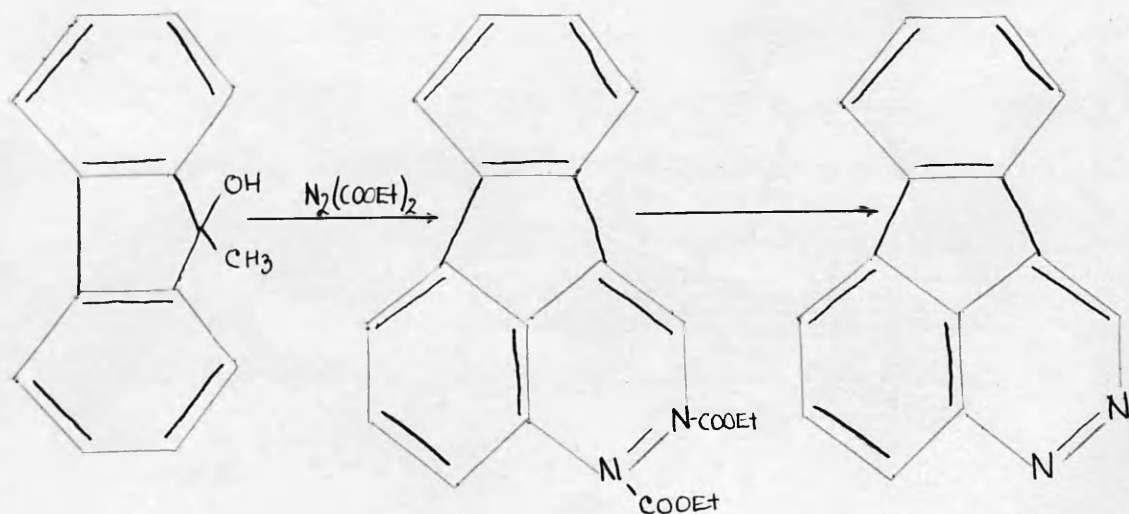
The initial problem was thus to improve upon the yields of fluoranthene-3:4-dicarboxylic acid anhydride.

No matter how the conditions of the Diels-Alder addition were varied, it was found impossible to obtain any increase in the 10% yield claimed by the above workers. The variations tried were changing concentration of acetic anhydride, changing the duration of the experiment, and finally the addition of trichloroacetic acid in an effort to catalyze the reaction.

On hydrolysis and decarboxylation of the acid anhydride, it was found that only a small amount of acid material was obtained.

This was in agreement with the work previously quoted but the very low yields rendered the subsequent synthesis of 3-methoxyfluoranthene impracticable.

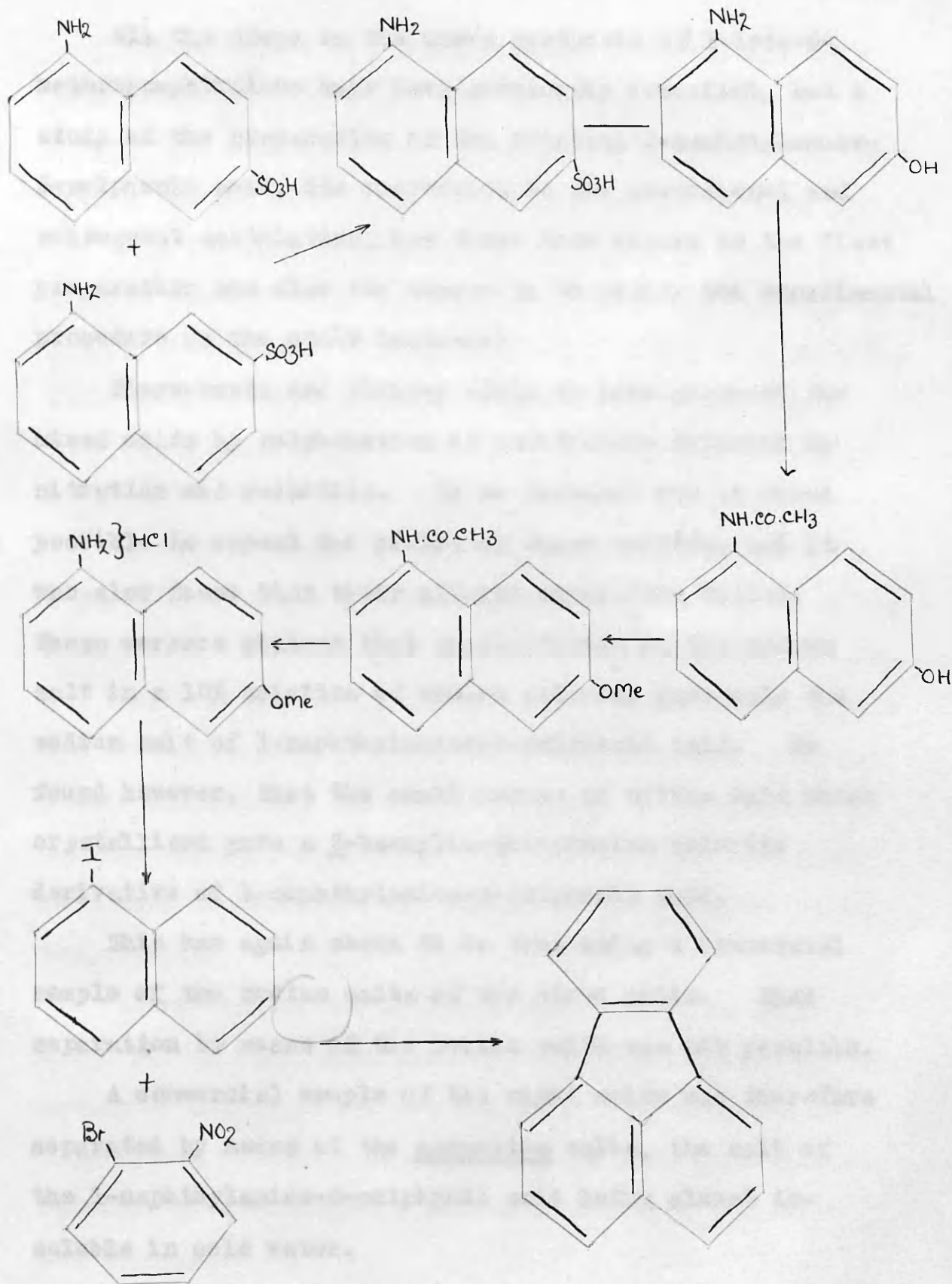
Using a synthesis analogous to that employed by Campbell and Wang it was thought that 3:4-diazafluoranthene might be synthesised.



It was however found impossible to form the Diels-Alder adduct at all using azo-dicarbethoxylate as the dienophile.

Thus both these approaches had to be abandoned, and in a further attempt to prepare 3-methoxyfluoranthene Cleves' acid was used as starting material.

By analogy to the work of Stubbs and Tucker(89) the synthesis of 3-methoxyfluoranthene should involve the condensation of o-bromonitrobenzene with 1-iodo-6-methoxynaphthalene. The difficulty is that 1-iodo-6-methoxynaphthalene cannot be prepared directly. Hence the rather devious route from Cleves' acid was undertaken. Cleves' acid is in fact a mixture of 1-naphthylamine-6-sulphonic acid and 1-naphthylamine-7-sulphonic acid. Thus the Cleves' acid must initially be separated to obtain only the 1-naphthylamine-6-sulphonic acid. The reaction sequence is shown overleaf.



All the steps in the above synthesis of 1-iodo-6-methoxynaphthalene have been previously described, but a study of the preparation of the original 1-naphthylamine-6-sulphonic acid, its conversion to the aminophenol and subsequent acetylation, has shown some errors in the first preparation and also the necessity to modify the experimental procedure in the other instances.

Fierz-David and Blangey claim to have prepared the mixed acids by sulphonation of naphthalene followed by nitration and reduction. In no instance was it found possible to repeat the yields of these workers, and it was also found that their alleged separation failed. These workers claimed that precipitation of the sodium salt in a 10% solution of sodium chloride gave only the sodium salt of 1-naphthylamine-7-sulphonic acid. We found however, that the small amount of sodium salt which crystallised gave a S-benzylisothiuronium chloride derivative of 1-naphthylamine-6-sulphonic acid.

This was again shown to be true using a commercial sample of the sodium salts of the mixed acids. Thus separation by means of the sodium salts was not possible.

A commercial sample of the mixed acids was therefore separated by means of the magnesium salts, the salt of the 1-naphthylamine-6-sulphonic acid being almost insoluble in cold water.

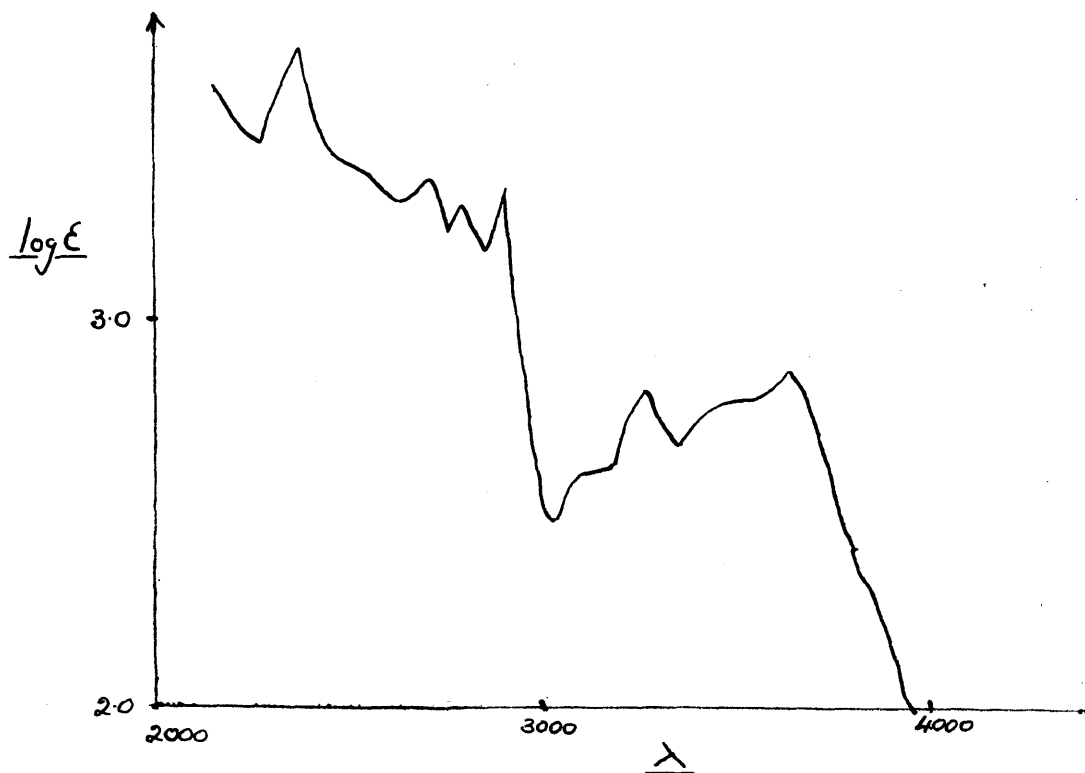
The conversion of 1-naphthylamine-6-sulphonic acid to 5-amino-2-naphthol has been described by Campbell, Laforge and Campbell(91). They used a melt of potassium hydroxide at a commencing temperature of 230°C, raising the melt to 310-320°C for about ten minutes. The yield claimed was 60%. It has been found however, that beyond 290°C, considerable decomposition occurs and also that the total time of heating should not exceed seven minutes. Thus, by a modified procedure we have obtained yields of 90%.

The above mentioned workers acetylated the 5-amino-2-naphthol by means of an unusually large excess of acetic anhydride. The reaction was kept cold and the time taken was four hours. The yield was 60%. The difficulty here was the separation of the product from the vast excess of acetic anhydride. It was found that, by acetylation in benzene solution as described by Kaufmann(92), the time necessary for reaction was fifteen minutes and the yield theoretical.

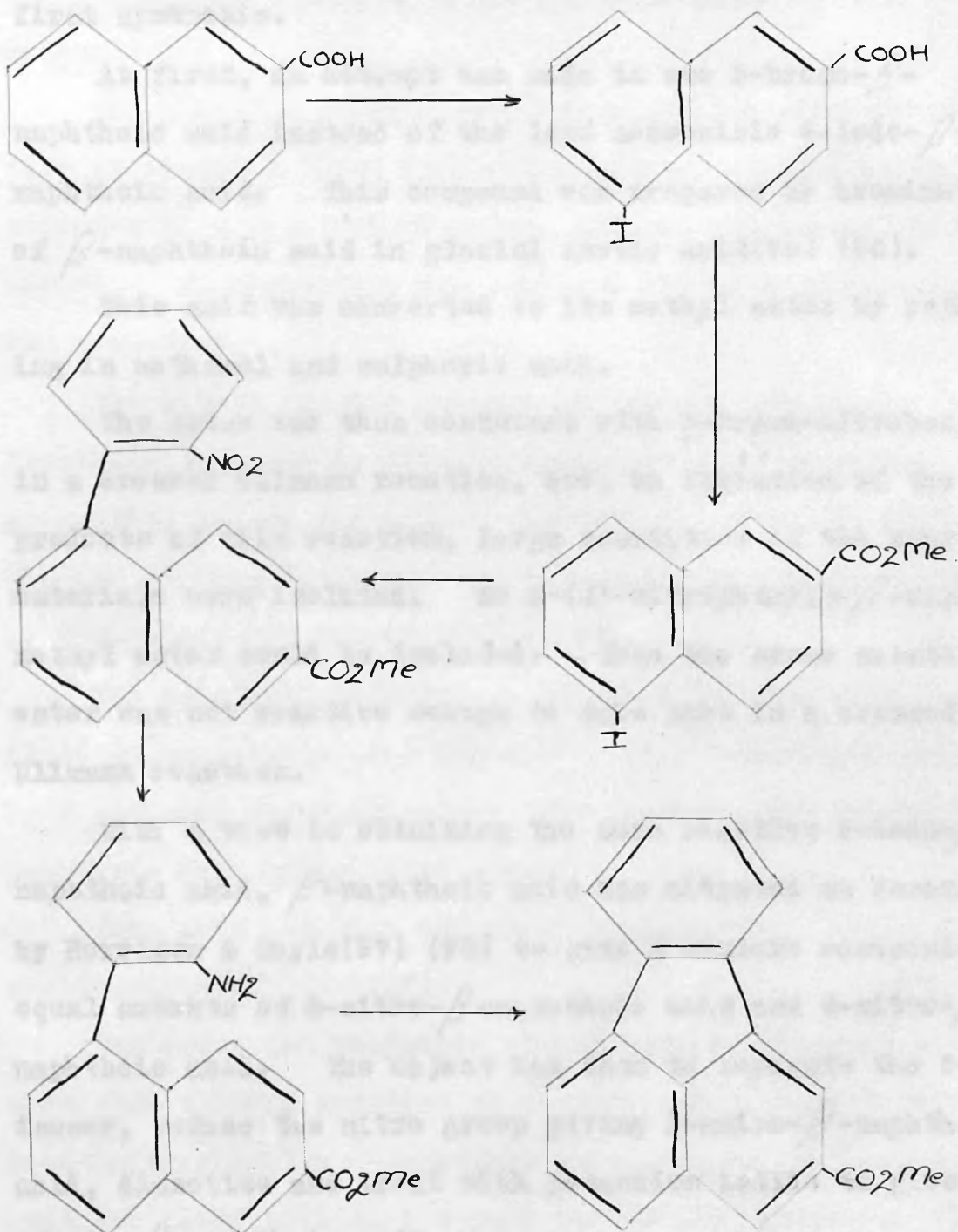
Conversion of the 5-acetylamino-2-naphthol to 6-methoxy-1-naphthylamine hydrochloride was effected by the method of Butenandt and Schramm(93). The compound 1-iodo-6-methoxynaphthalene was obtained from this hydrochloride by a Sandmeyer reaction as described by Wilds and Close(94).

3-Methoxyfluoranthene was prepared from 1-iodo-6-methoxynaphthalene as previously shown, the methods used being analogous to those employed previously by Stubbs & Tucker(89) for the synthesis of 4-methoxyfluoranthene. The product, 3-methoxyfluoranthene, has been characterised by several derivatives.

The ultra-violet spectrum of this compound conforms to the spectra obtained by Stubbs & Tucker for the 2-, and 4-methoxyfluoranthenes and does further support the theory put forward by these workers regarding the inter-relation of the p-bands and the position of the methoxyl group on the fluoranthene nucleus.



An attempt was also made to synthesise 3-methoxy-fluoranthene by a different route.





The ester thus obtained should then be readily converted to the methyl ether by the route shown in the first synthesis.

At first, an attempt was made to use 5-bromo- $\beta$ -naphthoic acid instead of the less accessible 5-iodo- $\beta$ -naphthoic acid. This compound was prepared by bromination of  $\beta$ -naphthoic acid in glacial acetic acid(95) (96).

This acid was converted to its methyl ester by refluxing in methanol and sulphuric acid.

The ester was then condensed with o-bromo-nitrobenzene in a crossed Ullmann reaction, but, on isolation of the products of this reaction, large quantities of the starting materials were isolated. No 5-(2'-nitrophenyl)- $\beta$ -naphthoic methyl ester could be isolated. Thus the bromo substituted ester was not reactive enough to take part in a crossed Ullmann reaction.

With a view to obtaining the more reactive 5-iodo- $\beta$ -naphthoic acid,  $\beta$ -naphthoic acid was nitrated as described by Horrison & Royle(97) (98) to give a mixture containing equal amounts of 5-nitro- $\beta$ -naphthoic acid and 8-nitro- $\beta$ -naphthoic acid. The object was then to separate the 5-isomer, reduce the nitro group giving 5-amino- $\beta$ -naphthoic acid, diazotize and treat with potassium iodide to give 5-iodo- $\beta$ -naphthoic acid.

A separation of the 5- and 8-nitro- $\beta$ -naphthoic acids is described in the literature(97) (99) whereby the mixture

of acids is treated with sodium carbonate solution, and, on concentrating the solution, the 5-isomer separates. The author was unable to achieve a separation by this method.

The ammonium salts were prepared and an attempt was made to separate these by chromatography, using a cellulose column with a solution of water, alcohol and ammonia as eluent. No separation was achieved and this preparation was abandoned.

The method finally adopted to prepare 5-iodo- $\beta$ -naphthoic acid was by direct iodination of  $\beta$ -naphthoic acid using iodine and silver sulphate in sulphuric acid. The use of these reagents for iodination was first described by Derbyshire and Waters(100) (101).

The 5-iodo- $\beta$ -naphthoic acid was separated from 5:8-diiodo- $\beta$ -naphthoic acid and unreacted  $\beta$ -naphthoic acid by fractional crystallisation from acetone, the 5-iodo- $\beta$ -naphthoic acid being least soluble.

This acid was then converted to its methyl ester as previously described(102).

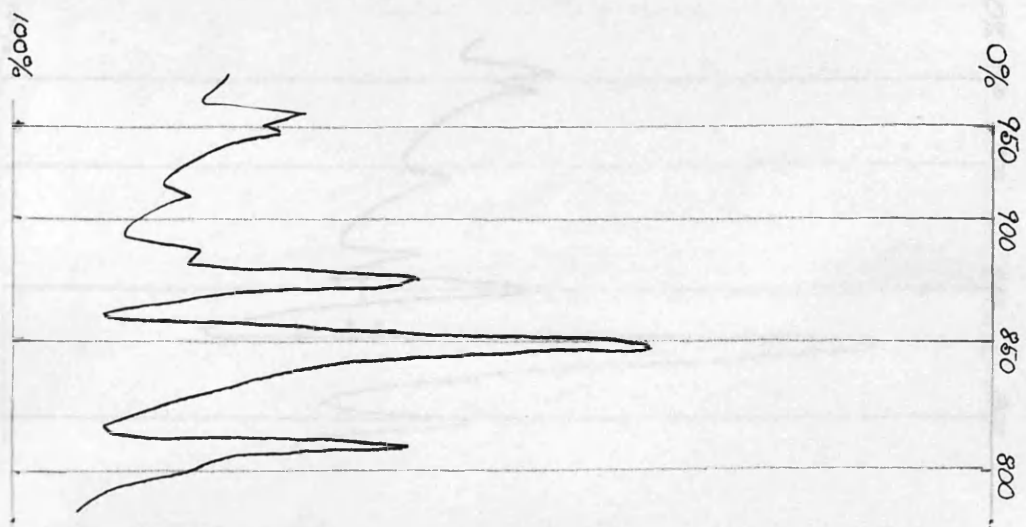
The ester was condensed with o-bromo-nitrobenzene by a crossed Ullmann reaction to yield a small quantity of 5-(2'-nitrophenyl)- $\beta$ -naphthoic ester. The reaction was repeated using activated copper powder(103) giving a greatly increased yield of the desired product.

Reduction of the nitro group with hydrogen and Raney nickel gave 5-(2'-aminophenyl)- $\beta$ -naphthoic methyl ester. Diazotisation of this amine and subsequent warming gave 3-carbomethoxyfluoranthene. By careful crystallisation, another compound was also isolated from this reaction. This compound had a much higher melting point. The exact nature of this is unknown but since the reaction used involves free radicals it is suggested that some form of dimeric material has resulted.

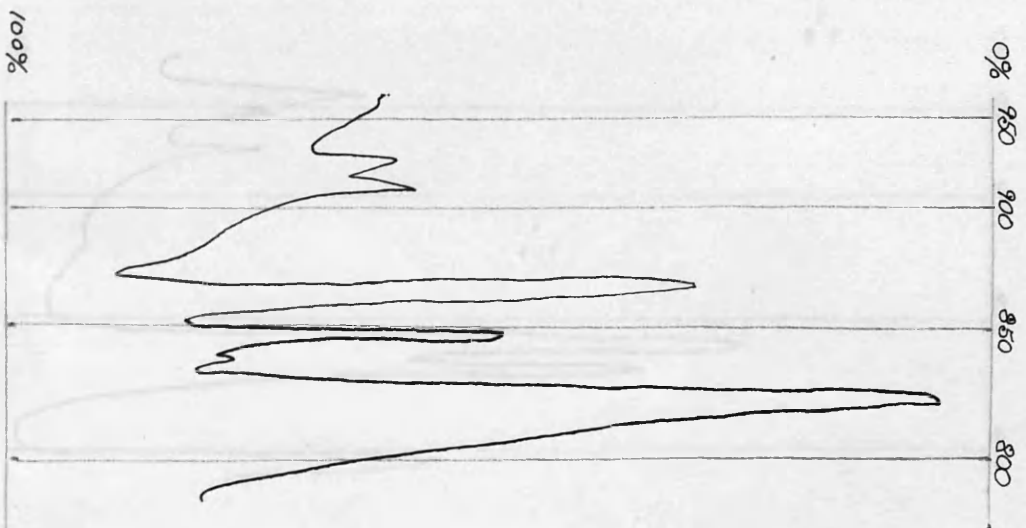
Further work is still being carried out on this synthesis of 3-methoxyfluoranthene with a view to publishing both syntheses of this compound.

The infra-red spectra of all the methoxyfluoranthenes and the two compounds synthesised above were now examined. For comparison 4-iodofluoranthene and 1-(o-methoxyphenyl) naphthalene were also examined. The graphs of these compounds between the wave-numbers of 1000 and 800 are shown.

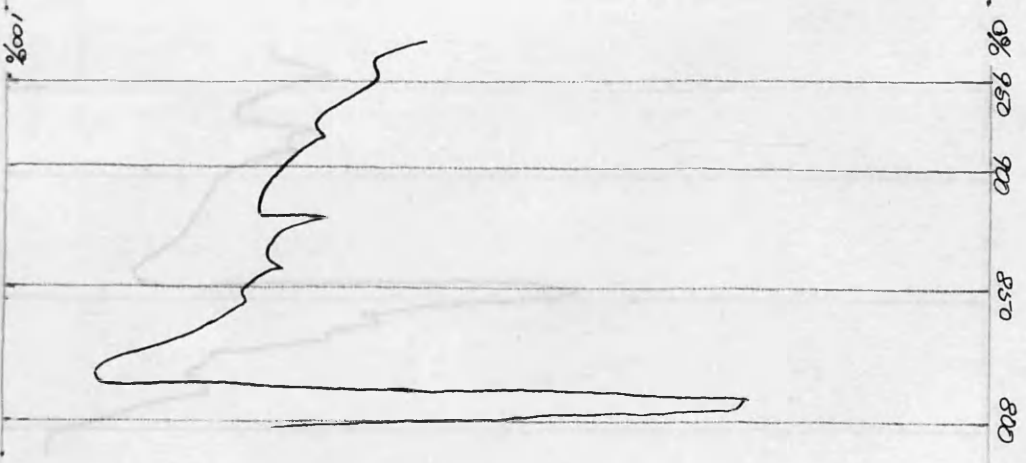
3-METHOXYFLUORANTHENE



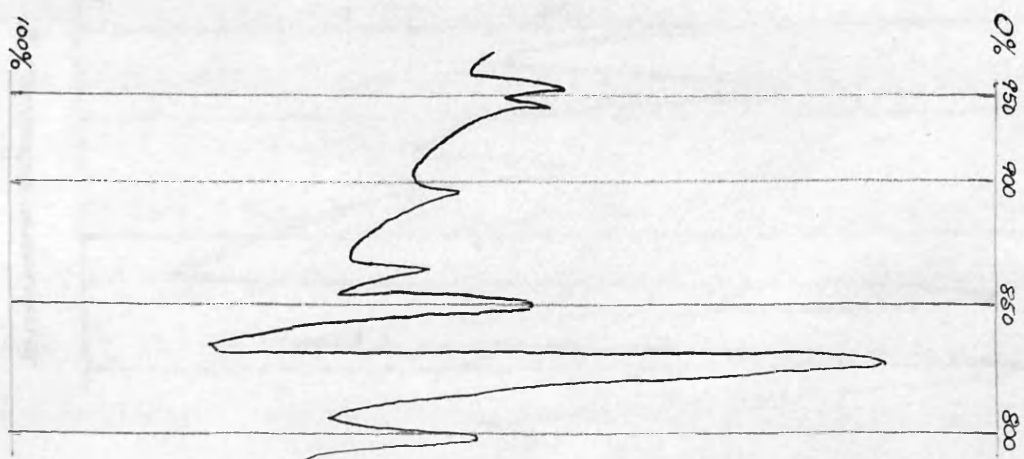
11-METHOXYFLUORANTHENE



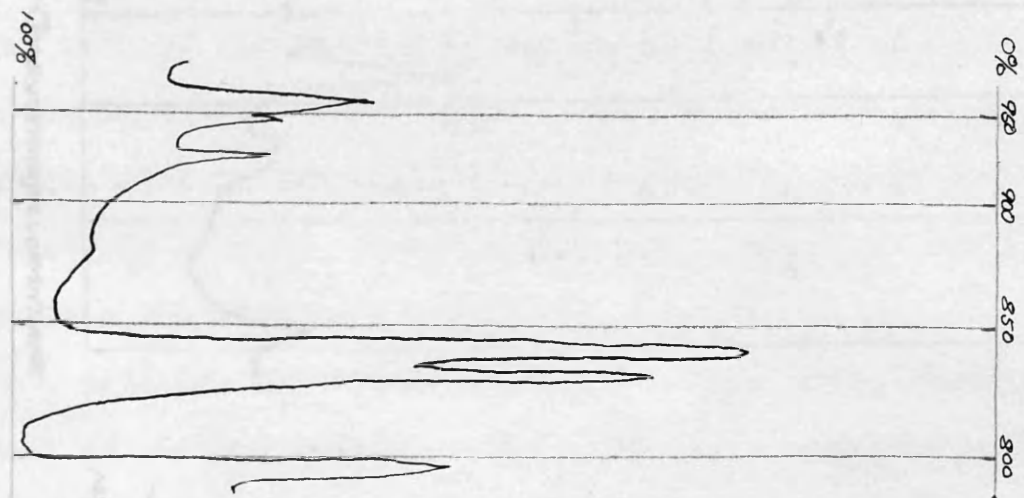
1-(2-Methoxyphenyl)naphthalene



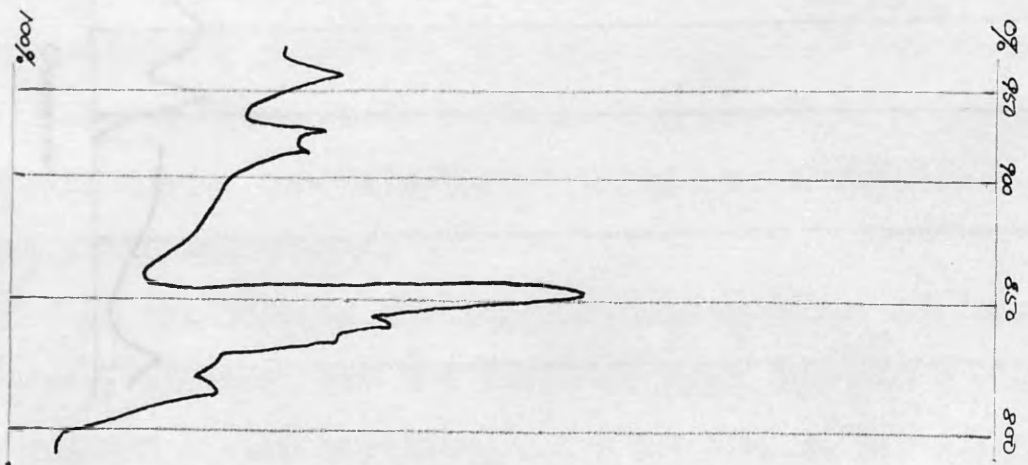
10-METHOXYFLUORANTHENE



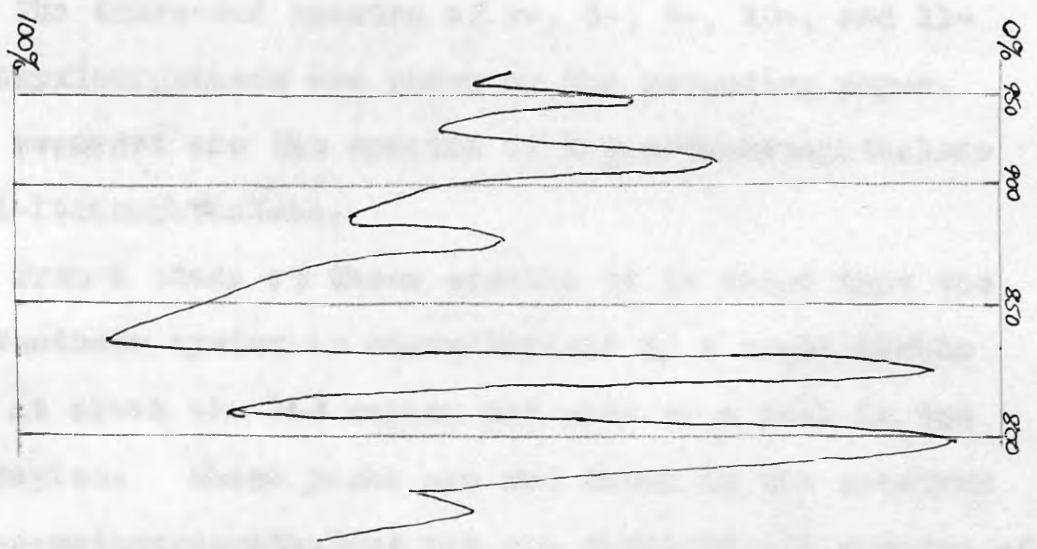
4-METHOXYFLUORANTHENE



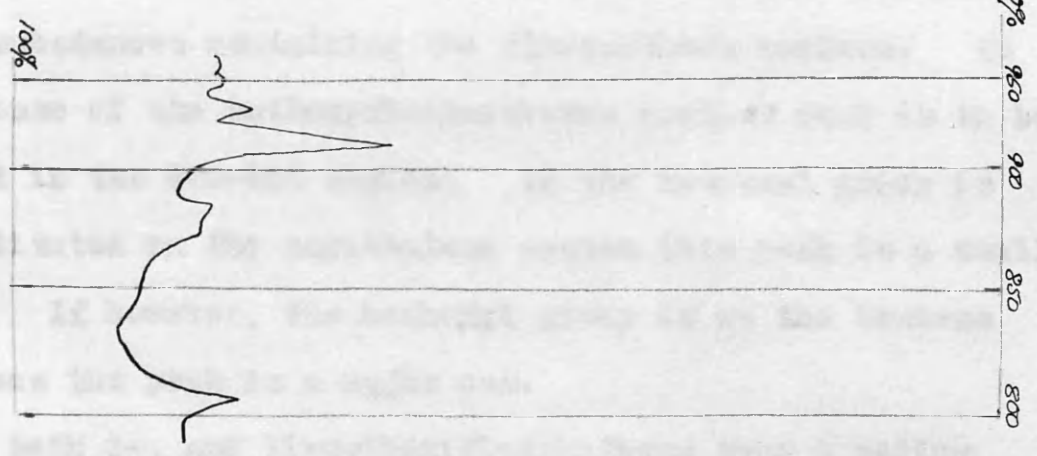
4-TRIFLUOROMETHYLFLUORANTHENE



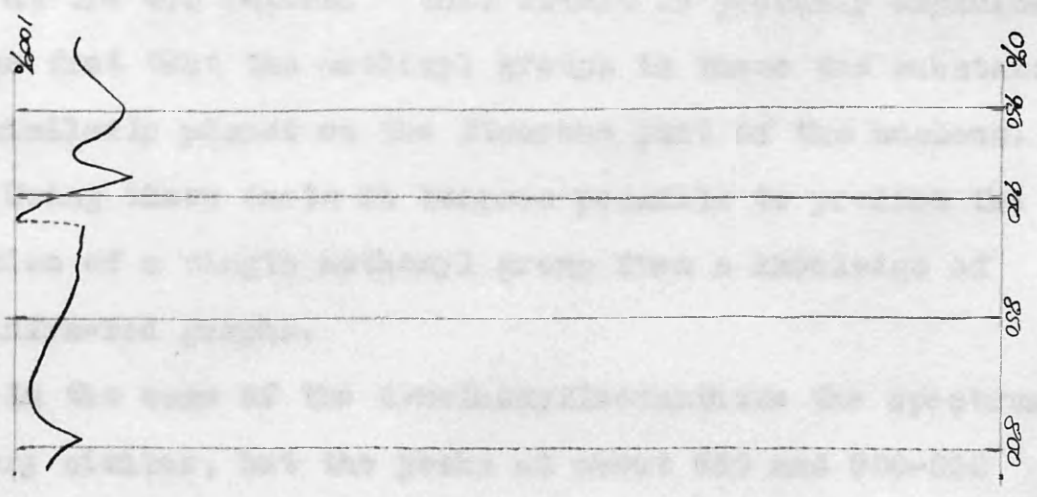
2. METHOXYFLUORANTHENE



3. CARBOMETHOXYFLUORANTHENE



UNKNOWN



The infra-red spectra of 2-, 3-, 4-, 10-, and 11-methoxyfluoranthene are shown on the preceding pages. Also recorded are the spectra of 1-o-methoxynaphthalene and 4-iodonaphthalene.

From a study of these spectra it is found that the fluoranthene system is characterised by a small double peak at about the 950 region and also by a peak in the 850 region. These peaks are not found in the spectrum of 1-o-methoxynaphthalene but are found in all spectra of the substances containing the fluoranthene nucleus. In the case of the methoxyfluoranthenes another peak is to be noted in the 800-820 region. If the methoxyl group is substituted on the naphthalene system this peak is a small one. If however, the methoxyl group is on the benzene nucleus the peak is a major one.

Both 3-, and 11-methoxyfluoranthene show a medium peak at the 875 region. This effect is probably explained by the fact that the methoxyl groups in these two substances are similarly placed on the fluorene part of the nucleus.

Using these facts it becomes possible to predict the position of a single methoxyl group from a knowledge of the infra-red graphs.

In the case of the 2-methoxyfluoranthene the spectrum is very similar, but the peaks at about 850 and 800-820 are moved closer together, being in fact at 830 and 810 respectively; also, the peaks are of almost identical intensity.

Thus, as was recorded by Stubbs and Tucker in their studies of the ultra-violet spectra of these compounds, the absorption spectrum of 2-methoxyfluoranthene does show a somewhat anomolous pattern.

The graphs of the carbomethoxy compounds are somewhat different, although in the case of 3-carbomethoxy-fluoranthene there is still a double peak in the 950 region with small peaks at 875 and 820. This is very similar to the spectrum of 3-methoxyfluoranthene.

The spectrum given by the material which had been suggested as a dimerised compound shows few peaks in this region and the infra-red spectrum does not seem in keeping with the complexity of the suggested formula.

A determination of the molecular weight by the Rast method also indicated that the product had a molecular weight of about 260, i.e. it was monomeric. The exact nature of this product has not been definitely established.



### EXPERIMENTAL

Fluoranthene-3:4-dicarboxylic acid anhydride.- As in the method of Campbell and Wang(87), 9-methylfluorenol (1.0 g.) was mixed with maleic anhydride (2.5 g.) in acetic anhydride (6.75 ml.) as solvent, and the mixture refluxed for two hours. Fluoranthene-3:4-dicarboxylic acid anhydride separated on cooling and crystallised from acetic anhydride in yellow needles m.p.  $268^{\circ}\text{C}$  (0.13 g. 10%).

Modified Procedure.- 9-Methylfluorenol (1.0 g.) was mixed with maleic anhydride (0.75 g.) and heated in acetic anhydride (10 ml.) under reflux for half an hour. The solution became almost black. On cooling, Fluoranthene-3:4-dicarboxylic acid anhydride separated as yellow needles m.p.  $268^{\circ}\text{C}$  (0.14 g. 10%).

Both these procedures were repeated using reaction times of four and six hours. The results were exactly as above. The six experiments above were repeated in the presence of trichloroacetic acid in an effort to catalyse the Diels-Alder reaction. In every case the yield remained at 10%.

Attempts to obtain more material from the reaction mixture by dilution with water always gave precipitation of the polymer derived from methylene fluorene.

3:4-Dicarbethoxy-3:4-diaza-3:4-dihydrofluoranthene.- 9-Methylfluorenol (1.0 g.) was mixed with ethyl-azodicarb-

oxylate (1.0 g.) and the mixture was heated at 130°C for 3 hours. The only product obtained was an intractible brownish coloured resin.

Modified Procedure.- (a) 9-Methylfluoreno1 (1.0 g.) was mixed with ethyl-azodicarboxylate (1.0 g.) in acetic anhydride (10 ml.) and the whole refluxed for 4 hours. The acetic anhydride was distilled off and the residue treated with caustic soda solution. The product was extracted with ether. This extract yielded only a gummy residue which appeared to be polymerised methylene-fluorene. It contained no nitrogen.

(b) The above experiment was repeated in the presence of trichloroacetic acid as catalyst. Again only polymer resulted.

Separation of the mixed 1-naphthylamine-6-sulphonic and 1-naphthylamine-7-sulphonic acids.- The commercial mixed acids (223 g.) were dissolved in water (2 l.) made alkaline with caustic soda solution (95 ml. 32%). Animal charcoal was added and the mixture stirred at 80-90°C for thirty minutes. The insoluble matter was filtered off and washed with boiling water (200 ml.). The volume was adjusted to 2,200 ml. and the solution stirred at 80-90°C while Epsom salt (367 g.) was added. The solution was allowed to cool slowly and the magnesium salt of 1-naphthylamine-6-sulphonic acid was filtered off.

This salt was dissolved in water at 80-90°C (2.5 l.) and hydrochloric acid (140 ml. 36%) was slowly added. On cooling, the 1-naphthylamine-6-sulphonic acid was filtered off. The compound was washed with water (500 ml.) and dried at 60°C. This gave 1-naphthylamine-6-sulphonic acid as a pink powder, (104 g. 60%).

5-Amino-2-naphthol.- 1-Naphthylamine-6-sulphonic acid (40 g.) was added to a melt of potassium hydroxide (70 g.) and water (10 ml.) at a temperature of 250°C. The temperature of the reaction mixture rose rapidly to 270-280°C. The mixture was maintained at this temperature so that the total reaction time was seven minutes; care being taken to avoid exceeding the critical temperature of 290°C, beyond which decomposition with evolution of ammonia occurred. Heating at the upper limit was however essential, otherwise much of the 1-naphthylamine-6-sulphonic acid was recovered unchanged. The fused mass was dissolved in hot water (250 ml.) and acidified with 5-N hydrochloric acid. The solution was filtered to remove tars, then just neutralised with caustic soda solution (15-N) and finally made alkaline with excess ammonium carbonate. This yielded 5-amino-2-naphthol as a grey powder m.p. 186°C (25.2 g. 90%).

5-Acetylamino-2-naphthol.- 5-Amino-2-naphthol (16.0 g.) was suspended in benzene (30 ml.). To the gently refluxing suspension was added the calculated equivalent of acetic anhydride. A vigorous reaction occurred to

yield a dark grey solid. This product, crystallised from methanol, yielded 5-acetylamino-2-naphthol as white blades, m.p. 215°C (yield theoretical).

The next stages of the synthesis of 1-iodo-6-methoxy-fluoranthene were carried out exactly as described in the literature.

2-Methoxy-5-(2'-nitrophenyl)naphthalene.- 1-Iodo-6-methoxy-naphthalene (2.8 g.) and o-bromonitrobenzene (2.2 g.) were heated to 180°C and copper powder (3.5 g.) added, with stirring. After 2 hours' heating the cooled mass was extracted with benzene. On evaporation the benzene yielded a red oil, which on trituration with ethanol followed by crystallisation from light petroleum (40-60°C) gave green-yellow prisms, m.p. 107-8°C, of 2-methoxy-5-(2'-nitrophenyl)naphthalene (0.8 g. 30%). (Found: C, 72.91: H, 4.87: N, 4.97.  $C_{17}H_{13}O_3N$  requires C, 73.1: H, 4.7: N, 5.6%).

2-Methoxy-5-(2'-aminophenyl)naphthalene.- Reduction of the above nitro compound with hydrogen in presence of Raney nickel in ethanol gave 2-methoxy-5-(2'-aminophenyl)naphthalene, m.p. 114°C (from ethanol), (c.a. 100%) (Found: C, 81.68: H, 5.93: N, 5.69.  $C_{17}H_{15}ON$  requires C, 81.9: H, 6.1: N, 5.6%).

3-Methoxyfluoranthene.- The above amine was dissolved in excess of hot dilute sulphuric acid, and the solution cooled

slowly, to give the sulphate as a white crystalline precipitate, which was then diazotised at room temperature, giving a red solution. After 30 minutes at room temperature the mixture was heated on a steam bath with frequent stirring, until it became colourless. The filtered residue was extracted with hot benzene, and the solution chromatographed on alumina. The yellow eluate (strong blue fluorescence) gave 3-methoxyfluoranthene (50%), which crystallised from methanol as cream micro-crystals, m.p.  $82^{\circ}\text{C}$  (Found: C, 87.68; H, 5.26.  $\text{C}_{17}\text{H}_{12}\text{O}$  requires C, 87.9; H, 5.2%).

This product was characterised by the formation of three derivatives. It was converted to its picrate, orange-yellow needles (from ethanol), m.p.  $178^{\circ}\text{C}$  (softening at  $174^{\circ}\text{C}$ ) (Found: C, 59.67; H, 3.03; N, 8.97.  $\text{C}_{17}\text{H}_{12}\text{O} \cdot \text{C}_6\text{H}_3\text{O}_7\text{N}_3$  requires C, 59.9; H, 3.3; N, 9.1%). It also yielded a complex with 1:3:5-trinitrobenzene, which crystallised from a mixture of ethanol and acetic acid as yellow needles, m.p.  $177-178^{\circ}\text{C}$ . (Found: C, 61.9; H, 3.2.  $\text{C}_{17}\text{H}_{12}\text{O} \cdot \text{C}_6\text{H}_3\text{O}_6\text{N}_3$  requires C, 62.0; H, 3.4%). It was finally converted to a 2:4:7-trinitrofluorene complex (in glacial acetic acid) crystallising from glacial acetic acid in orange needles, m.p.  $220^{\circ}$  (Found: C, 65.8; H, 3.06.  $\text{C}_{17}\text{H}_{12}\text{O} \cdot \text{C}_{13}\text{H}_5\text{O}_7\text{N}_3$  requires C, 65.8; H, 3.1%).

5-Bromo- $\beta$ -naphthoic methyl ester.- The method used was the same as that used by Goldstein and Matthey(102) for the preparation of 5-iodo- $\beta$ -naphthoic acid.

5-Bromo- $\beta$ -naphthoic acid (0.8 g.) was refluxed for three hours with a mixture of methanol and concentrated sulphuric acid (20:1). Methanol was then removed by distillation and the ester obtained by pouring the mixture into water. Crystallisation of the crude product from 90% methanol gave 5-Bromo- $\beta$ -naphthoic methyl ester as white needles m.p. 72°C (0.6 g. 70%).

5-(2'-Nitrophenyl)- $\beta$ -naphthoic ester.- 5-Bromo- $\beta$ -naphthoic ester (0.46 g.) was heated in an oil bath at 180°C for one hour in the presence of o-bromo-nitrobenzene (0.33 g.) and copper powder (0.25 g.). The mixture was mechanically stirred. The product was extracted with hot benzene.

The benzene solution was chromatographed on alumina. The first fraction of the eluate contained o-bromo-nitrobenzene, and a later fraction the unchanged bromo-ester (0.4 g. 87%). None of the desired product was obtained.

5-Iodo- $\beta$ -naphthoic acid.- Silver sulphate (1.0 g.) was dissolved in sulphuric acid (40 ml. H<sub>2</sub>SO<sub>4</sub>/2 ml. water) contained in a round-bottomed flask, and the solution cooled to room temperature.  $\beta$ -Naphthoic acid (0.86 g.) and iodine (1.5 g.) were added and the whole stirred violently with a tantalum stirrer. After two hours carbon tetrachloride (40 ml.) was added and stirring

continued for one hour.

The solution was then poured into cold water (300 ml.) and the solids filtered off. More carbon tetrachloride was added to that contained in the filtrate, and the aqueous layer was separated and discarded.

The solids and the carbon tetrachloride were extracted with 5% potassium hydroxide and the extracts charcoaled. Acidification of the extract gave the crude acid. Crystallisation of this product from acetone gave 5-Iodo- $\beta$ -naphthoic acid as cream needles m.p.  $253^{\circ}\text{C}$  (1.0 g. 66%).

The methyl ester was again prepared by the action of methanol and concentrated sulphuric acid. This gave 5-Iodo- $\beta$ -naphthoic methyl ester as cream needles m.p.  $76^{\circ}\text{C}$  (1.1 g. 72%).

5-(2'-Nitrophenyl)- $\beta$ -naphthoic methyl ester.- 5-Iodo- $\beta$ -naphthoic methyl ester (1.57 g.) was heated at  $180^{\circ}\text{C}$  for one hour in the presence of o-bromo-nitrobenzene (1.01 g.) and activated copper powder (103) (0.8 g.), the mixture being vigorously stirred. The product was extracted with hot ethanol. On cooling, the extract yielded a yellow solid. Recrystallisation of this compound from ethanol gave 5-(2'-Nitrophenyl)- $\beta$ -naphthoic methyl ester as yellow rhombs m.p.  $170^{\circ}\text{C}$  (0.51 g. 33%) (Found: C, 70.17; H, 3.97; N, 4.74.  $\text{C}_{18}\text{H}_{13}\text{O}_4\text{N}$  requires C, 70.35; H, 4.26; N, 4.56%).

5-(2'-Aminophenyl)- $\beta$ -naphthoic methyl ester.- 5-(2'-Nitrophenyl)- $\beta$ -naphthoic methyl ester (0.89 g.) was catalytically reduced by hydrogen in the presence of Raney nickel catalyst. The solvent used in the reaction was ethanol/ethyl acetate (5:1). Theoretical absorption of hydrogen occurred in 2 hours. On filtering off the nickel and concentrating the solution a white solid was obtained. Recrystallisation from ethanol gave 5-(2'-Aminophenyl)- $\beta$ -naphthoic methyl ester as white needles m.p. 146°C (0.64 g. 80%). (Found: C, 78.20; H, 5.72; N, 5.33.  $C_{18}H_{15}O_2N$  requires C, 77.96; H, 5.45; N, 5.05%).

3-Carbomethoxyfluoranthene.- 5-(2'-Aminophenyl)- $\beta$ -naphthoic methyl ester (0.4 g.) was dissolved in the minimum of warm dilute sulphuric acid (1 ml. sulphuric acid: 9 ml. of water) The solution was cooled to 0°C. A solution of sodium nitrite (0.13 g.) in water (5 ml.) was slowly added. The solution became slightly yellow on the addition of the nitrite. The solution was warmed on a steam bath for twenty minutes. A sandy-coloured solid was filtered off which on recrystallisation from acetic acid gave 3-Carbomethoxyfluoranthene as faintly brown needles m.p. 115°C. (Found: C, 82.66; H, 4.81.  $C_{18}H_{12}O_2$  requires C, 83.06; H, 4.65%).

Another product was also isolated from the crude product by crystallisation from ethyl acetate to give faintly brown crystals m.p. 282°C. (Found: C, 82.82; H, 4.45.  $C_{36}H_{26}O_4$  requires C, 82.7; H, 5.01%).



SUMMARY

3-Methoxyfluoranthene has been synthesised from Cleves acid using a method similar to that of Stubbs and Tucker. A further synthesis has yielded 3-Carbo-methoxyfluoranthene and work is being continued to convert this compound into 3-Methoxyfluoranthene.

The infra-red spectra of the methoxyfluoranthenes are shown and an attempt has been made to relate position of substitution to the spectrum produced.

The ultra-violet spectrum of 3-Methoxyfluoranthene has been shown to conform to the principles of the substitution/spectrum relationship discussed by Stubbs and Tucker(89).

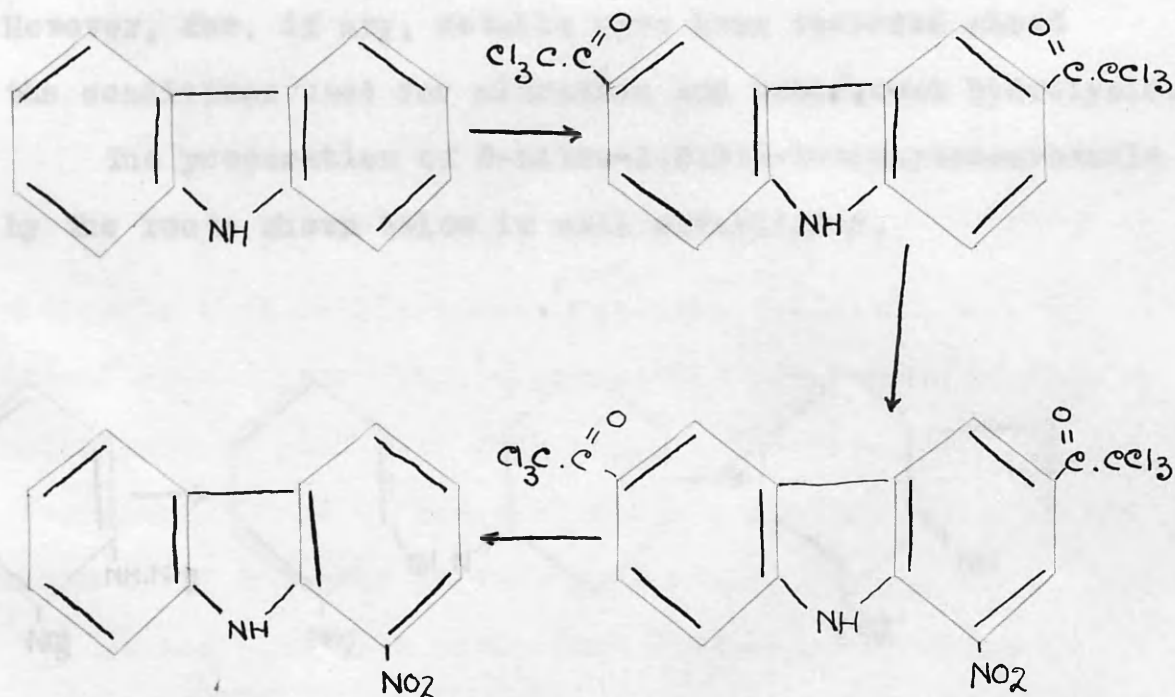
PART IV

"1-NITROCARBAZOLE AND SOME DERIVATIVES  
OBTAINED FROM IT BY THE ULLMANN REACTION"

## INTRODUCTION

Nitration of carbazole does not give a single product - two isomers are produced(104). The yield of 1-nitrocarbazole from direct nitration was always very low, and the compound was only obtained pure by a tedious process.

Later workers(38) succeeded in separating 1-nitrocarbazole and 3-nitrocarbazole by chromatography. These workers also synthesised 1-nitrocarbazole as show below.



This method had the advantage that there was no possibility of 3-nitrocarbazole being formed. Independently Campbell and MacLean(107) also prepared 1-nitrocarbazole by nitration of 3:6-dibromocarbazole.

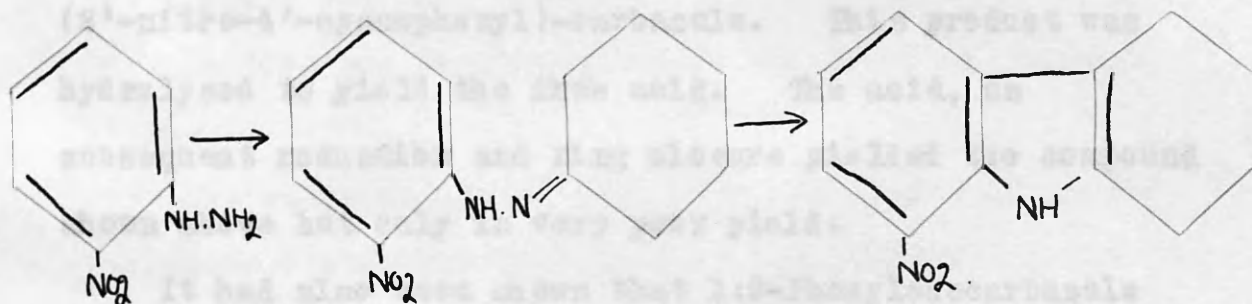
This method of blocking the 3- and 6- positions has been the basis of many processes for the formation

of 1-nitrocarbazole. The blocking group generally used was the sulphonic group(105) (106).

The sulphonation method introduced the difficulty of very high melting products with no sharp melting point. However, both Carbazole-3:6-disulphonic acid and Carbazole-3:6:8-trisulphonic acid have been prepared.

In the processes mentioned(105) (106), it was claimed that nitration of these sulphonic acids and subsequent desulphonation yielded 1-nitrocarbazole in good yield. However, few, if any, details have been recorded about the conditions used for nitration and subsequent hydrolysis.

The preparation of 8-nitro-1:2:3:4-tetrahydrocarbazole by the route shown below is well established,

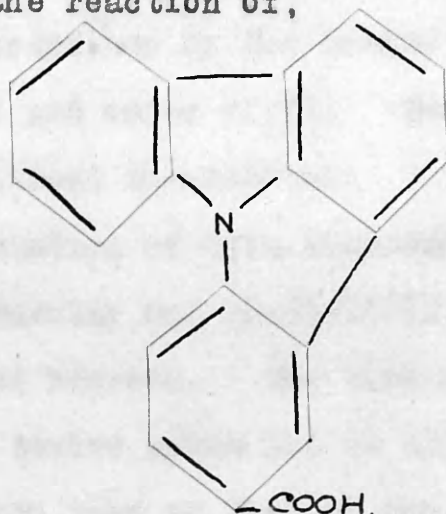


and the work of Barclay and Campbell(41) on the dehydrogenation of this compound, has shown this method to be the best preparation available.

The use of carbazole in Ullmann type reactions has been examined previously by Tucker(108) (109) in an effort to obtain optically active tervalent nitrogen compounds. By the Ullmann reaction and subsequent Pschorr

cyclisation a number of 1:9-Phenylencarbazoles have been prepared but at no time was it possible to synthesise such a compound with a substituent placed unsymmetrically upon it.

An attempt was made to prepare the compound shown below(108) by the reaction of,



carbazole with 4-chloro-3-nitrobenzonitrile to yield 9-(2'-nitro-4'-cyanophenyl)-carbazole. This product was hydrolysed to yield the free acid. The acid, on subsequent reduction and ring closure yielded the compound shown above but only in very poor yield.

It had also been shown that 1:9-Phenylencarbazole could be prepared using 1-nitrocarbazole as starting material(109). This showed that it was possible to effect ring closure in the opposite direction to that used in the previous paper. For this reason it was decided to attempt the preparation of 1:9-Phenylencarbazole-4'-carboxylic acid using 1-nitrocarbazole as starting material.

### DISCUSSION

An attempt was first made to prepare 1-nitrocarbazole by the Borsche type synthesis from the o-nitrophenylhydrazone of cyclohexanone.

The tetrahydrocarbazole was obtained from cyclohexanone o-nitrophenylhydrazone by the action of a mixture of sulphuric acid and water (1:9). The yield obtained in this way was almost theoretical.

Dehydrogenation of this compound was carried out as described by Barclay and Campbell(41). A slight modification was used however. The time of reaction was varied from three to twelve hours but in all cases the yield obtained was the same as that of the previous workers. The product was most readily purified by chromatography.

In this way 1-nitrocarbazole was obtained in good yield.

The sulphonation of carbazole was also attempted. Carbazole-3:6:8-trisulphonic acid was prepared by the action of concentrated sulphuric and mercuric sulphate on carbazole. The product was isolated as its potassium salt.

Carbazole-3:6-disulphonic acid was prepared by the method of Schultz and Hauenstein(106) and was again isolated as its potassium salt.

In both cases an attempt was made to nitrate the sulphonic acids without isolation(106).

According to the literature this nitration should go to completion but later work showed that only partial nitration had occurred with the carbazole-3:6:8-trisulphonic acid and that in the other case no nitration occurred.

In the case of partial nitration it was found that hydrolysis in phosphoric acid at a temperature of 180°C in a pressure tube yielded a small amount of 1-nitrocarbazole. Along with this product was isolated a quantity of carbazole. In the other instance only carbazole was isolated after hydrolysis at a temperature of 180°C under pressure.

Nitration was then attempted using fuming nitric acid in acetic acid as solvent. Refluxing for three hours again gave no nitration. This was verified by hydrolysis of the resulting product to carbazole.

In a final attempt to nitrate carbazole-3:6-disulphonic acid, the compound was refluxed with fuming nitric for one hour. A cream white crystalline product resulted. This was 1:3:6:8-Tetranitrocarbazole.

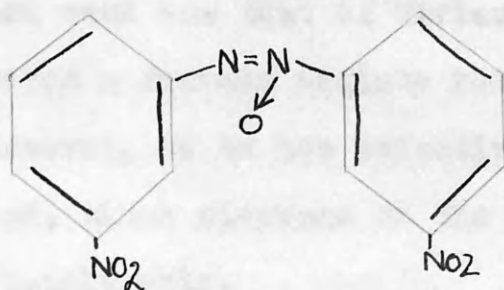
Thus it seems that a considerable amount of research into the nitration conditions used in the original papers is essential before this method can be used to prepare 1-nitrocarbazole.

1-Nitrocarbazole was then reacted with an excess *p*-iodo-benzoic methyl ester at 180°C in the presence of copper bronze and potassium carbonate. No reaction could be induced at this temperature even after heating for six hours. The temperature of the reaction was raised to 223°C. In this instance reaction did take place, and after six hours heating a black product was obtained, which, on careful crystallisation, yielded a small quantity of 1-nitro-9-(4'-carbomethoxyphenyl)carbazole. The yield of this compound was very low and from these reactions it does seem to indicate that this reaction can only be induced with great difficulty.

Using the method of Dunlop and Tucker(108) 9-(2'-nitrophenyl)carbazole was prepared and this was converted to the corresponding amine by reduction with hydrazine in the presence of Raney nickel(110). This gave an almost theoretical yield of the amine.

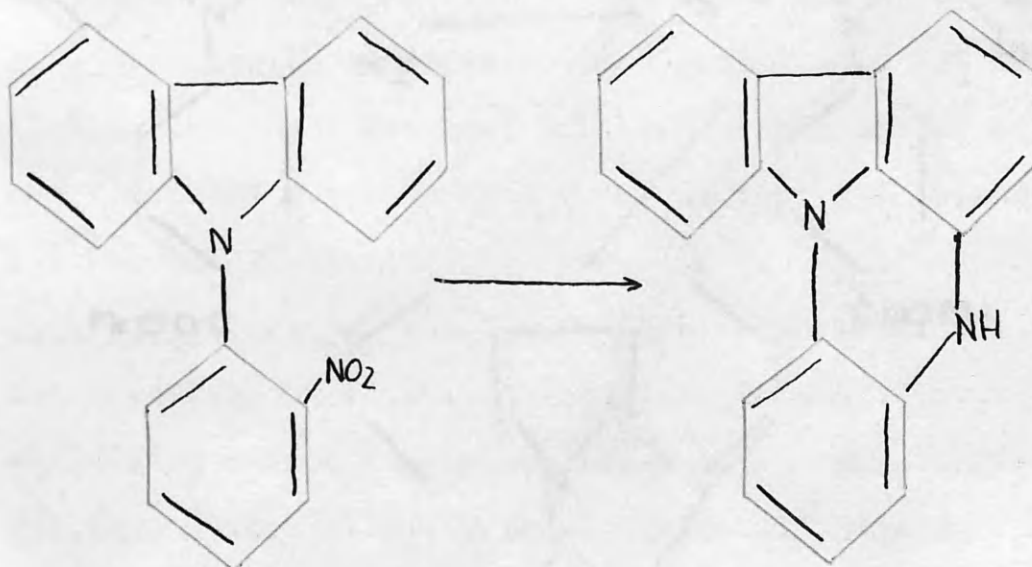
During the use of this method an investigation was made to see if this might be used to give the half reduction of a dinitro compound. Using the amount of hydrazine calculated for the reduction of only one nitro group, an attempt was made to prepare *m*-nitraniline from *m*-dinitrobenzene. The product obtained from this reaction was the azoxy benzene shown overleaf.





This is interesting since it does throw light on the route followed in this reduction. Whether or not this reaction can be used to give mono-reduction is not definitely proven, but by the isolation of this intermediate it does seem very likely that the use of a half mole excess of hydrazine could cause the necessary cleavage of the above azoxy compound.

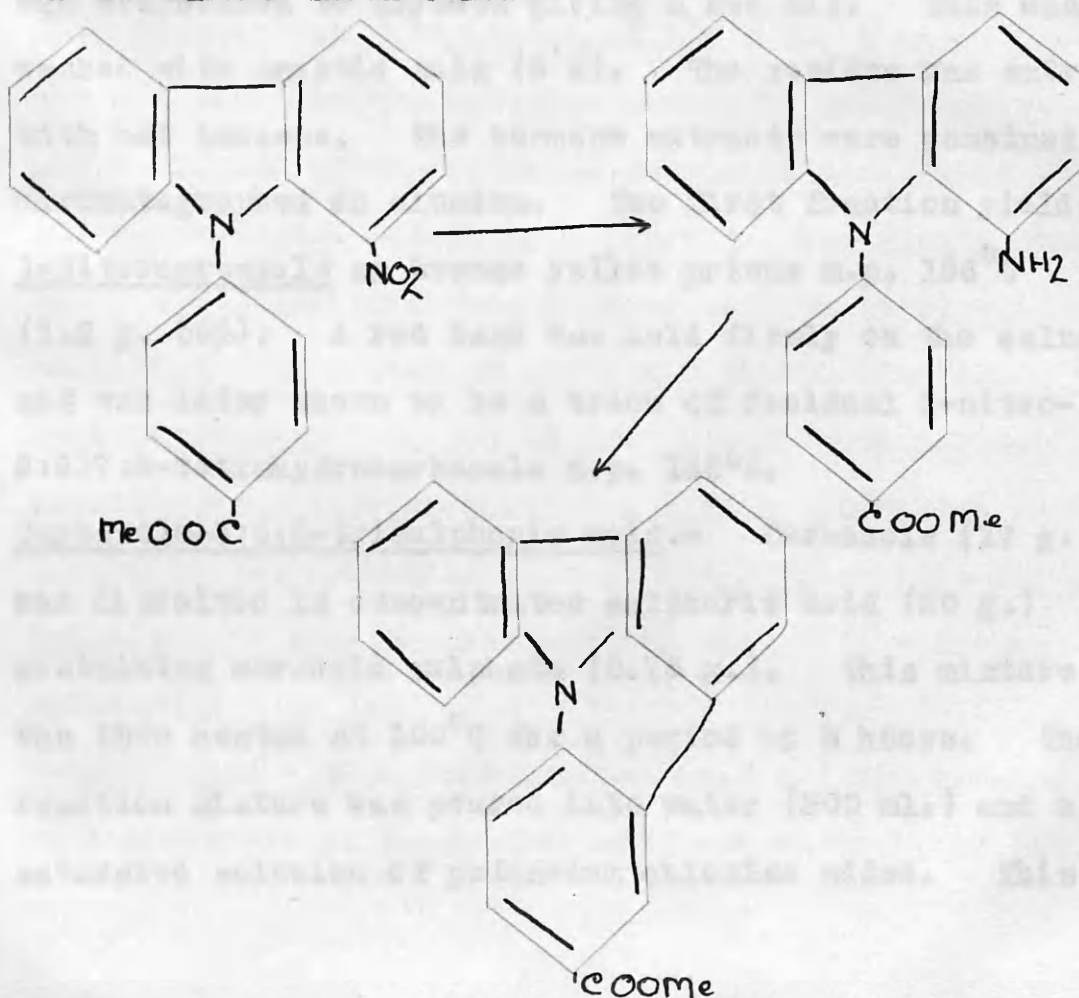
Using the compound 9-(2'-nitrophenyl)carbazole attempts were made to produce a phenazine as shown below.



The method used was that of Vivian and his co-workers(111) who employed a ferrous oxalate reduction. The system seems, however, to be too sensitive for this reaction to be applied, since cleavage of the molecule occurred to give carbazole only.

Attempts to use 1-nitro-9-phenyl-carbazole in this reaction also failed, 1-nitrocarbazole being formed in good yield.

In the time available it was not possible to proceed further with this work. It does seem likely, however, that the desired type of compound might be synthesised from 1-Nitro-9-phenyl-carbazole-4'-carboxylic methyl ester in the manner shown below.



EXPERIMENTAL

1-Nitro-5:6:7:8-tetrahydrocarbazole.- Cyclohexanone o-nitrophenylhydrazone (2.33 g.) was refluxed in a mixture of sulphuric acid and water (1:9) (50 ml.) for three hours. This yielded a dark red solid which on crystallisation from methanol gave 1-Nitro-5:6:7:8-tetrahydrocarbazole as red prisms m.p.  $148^{\circ}\text{C}$  (1.95 g. 90%).

1-Nitrocarbazole.- 1-Nitro-5:6:7:8-tetrahydrocarbazole (2.16 g.) and chloranil (5.4 g.) were refluxed in xylene (150 ml.) for 5 hours. The resulting dark solid was washed three times with warm caustic soda (5 N). The residue was extracted with benzene. The xylene solution was evaporated to dryness giving a red oil. This was washed with caustic soda (5 N). The residue was extracted with hot benzene. The benzene extracts were combined and chromatographed on alumina. The first fraction yielded 1-Nitrocarbazole as bronze yellow prisms m.p.  $186^{\circ}\text{C}$  (1.2 g. 56%). A red band was held firmly on the column and was later shown to be a trace of residual 1-nitro-5:6:7:8-tetrahydrocarbazole m.p.  $148^{\circ}\text{C}$ .

Carbazole-3:6:8-trisulphonic acid.- Carbazole (17 g.) was dissolved in concentrated sulphuric acid (50 g.) containing mercuric sulphate (0.15 g.). This mixture was then heated at  $100^{\circ}\text{C}$  for a period of 3 hours. The reaction mixture was poured into water (300 ml.) and a saturated solution of potassium chloride added. This

yielded Carbazole-3:6:8-trisulphonic acid as its potassium salt (35 g. 71%).

Carbazole-3:6-disulphonic acid.- Carbazole (17 g.) was dissolved in concentrated sulphuric acid (56 g.  $d = 1.84$ ) and heated for 30 minutes at  $100^{\circ}\text{C}$ . The mixture was cooled and poured into water (300 ml.). A saturated solution of potassium chloride was then added (200 ml.). On evaporation to half bulk the potassium salt of Carbazole-3:6-disulphonic acid was obtained as white prisms (26.2 g. 70%).

1-Nitrocarbazole-3:6:8-trisulphonic acid.- Carbazole (17 g.) was dissolved in concentrated sulphuric acid (50 g.) and mercuric sulphate (0.15 g.) was added. This mixture was then heated at  $100^{\circ}\text{C}$  for 3 hours. The reaction mixture was then cooled to room temperature and a mixture of concentrated sulphuric acid (11.6 g.) and concentrated nitric acid (11.6 g.) was slowly dropped in. The temperature was allowed to rise freely. The whole was then heated at  $100^{\circ}\text{C}$  for thirty minutes. The reaction mixture was poured into a saturated aqueous solution of potassium chloride. This yielded a small amount of the potassium salt of 1-nitrocarbazole-3:6:8-trisulphonic acid largely contaminated with starting material.

Hydrolysis.- The above product (2.7 g.) was treated with a mixture of phosphoric acid and water (1:1) (40 ml.)

in a sealed tube at  $180^{\circ}\text{C}$ . The product was extracted with benzene and evaporation of this extract gave a yellow solid which, on crystallisation from methanol gave a small amount of 1-Nitrocarbazole as yellow prisms m.p.  $186^{\circ}\text{C}$  (0.11 g. 10%).

1-Nitrocarbazole-3:6-disulphonic acid.- Carbazole (17 g.) was disulphonated by means of concentrated sulphuric acid as previously described. The sulphonation mixture was then nitrated using a mixture of concentrated sulphuric acid (11.6 g.) and concentrated nitric acid (11.6 g.) the whole being finally heated at  $100^{\circ}\text{C}$  for thirty minutes. This reaction mixture was poured into a saturated solution of potassium chloride to give a greenish-yellow product (40 g.). Treatment of this product (1.0 g.) with phosphoric acid at  $180^{\circ}\text{C}$  under a pressure of 8 atmospheres yielded carbazole only. Thus no nitration of the disulphonic acid had been effected. The weight of carbazole recovered was (0.4 g. 90%).

1-Nitrocarbazole-3:6-disulphonic acid.- The potassium salt of carbazole-3:6-disulphonic acid (3.8 g.) was suspended in acetic acid (100 ml.) and fuming nitric acid (1.0 g.) added. The mixture was refluxed for three hours. This yielded a light yellow solid (4.0 g.). Hydrolysis of this material at  $180^{\circ}\text{C}$  under a pressure of 8 atmospheres again showed that no

nitration had been effected since only carbazole was produced.

1:3:6:8-Tetranitrocarbazole.- The potassium salt of carbazole-3:6-disulphonic acid (3.8 g.) was added to fuming nitric acid (100 ml.) and the mixture was refluxed for  $1\frac{1}{2}$  hours. The mixture was cooled and allowed to evaporate slowly. This gave a cream solid, which, on recrystallisation from acetic acid gave 1:3:6:8-Tetranitrocarbazole as yellow prisms m.p.  $> 260^{\circ}\text{C}$  (explosion).

9-(2'-Aminophenyl)carbazole.- 9-(2-Nitrophenyl)carbazole (1.0 g.) was suspended in ethanol (50 ml.) and Raney nickel (1.0 g.) added. Hydrazine hydrate (1.0 ml.) was then introduced and the mixture warmed gently for one hour. The nickel was filtered off, and concentration gave 9-(2'-Aminophenyl)carbazole as cream needles m.p.  $121^{\circ}\text{C}$  (0.85 g. 96%).

2:2'-Dinitroazoxybenzene.- 1:3-Dinitrobenzene (1.0 g.) was dissolved in ethanol (50 ml.) and Raney nickel (0.5 g.) was added. Hydrazine hydrate (0.33 g.) was then introduced and the mixture was warmed gently for one hour. The nickel was filtered off and concentration of the yellow solution thus obtained gave 2:2'-Dinitroazoxybenzene as cream micro-crystals m.p.  $139^{\circ}\text{C}$ . (Found: C, 50.02; H, 3.04; N, 19.69.  $\text{C}_{12}\text{H}_8\text{O}_5\text{N}_4$  requires C, 50.00; H, 2.8; N, 19.44%).

1-Nitro-9-(4'-carbomethoxyphenyl)carbazole.- 1-Nitro-carbazole (1.0 g.) and p-iodo-methylbenzoate (2.5 g.) were heated in the presence of potassium carbonate (1.0 g.) and copper bronze (0.1 g.) for six hours at 223°C with constant stirring. The resulting product was steam distilled to remove p-iodo-methylbenzoate and the residue crystallised from methyl cyanide to yield 1-Nitro-9-(4'-carbomethoxyphenyl)carbazole as yellow plates m.p. 168°C (0.17 g. 10%) (Found: C, 69.59: H, 4.21: N, 8.00.  $C_{20}H_{14}O_4N_2$  requires C, 69.36: H, 4.07: N, 8.09%).

Ferrous oxalate reductions.- (a) 9-(2'-Nitrophenyl)carbazole (0.5 g.) was mixed with ferrous oxalate (0.7 g.) and heated to 270°C. The internal temperature rose rapidly to 300°C. Extraction of the cold product with acetone yielded carbazole (0.25 g. 70%).

(b) 1-Nitro-9-phenylcarbazole (0.5 g.) was mixed with ferrous oxalate (0.7 g.) and the mixture heated to 270°C. The temperature again rose rapidly to 300°C. Extraction of the cold product with acetone gave a yellow solution. This was evaporated and the yellow product crystallised from methanol to give 1-nitrocarbazole as yellow prisms m.p. 186°C.

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